Panic, phobia and hypocapnia

PANIC, PHOBIA AND HYPOCAPNIA

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Proefschrift

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Gerda Margo van der Molen

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Wanneer ik mij hier aan een psychologisch onderzoek naar het wezen van de angst waag, ben ik er mij dan ook van bewust een onderwerp te entameren, dat een geschenk is van de cultuurfase waarin ik leef, en in het bijzonder van bepaalde psychologische stromingen, die voor deze fase bij uitstek kenmerkend mogen worden geacht.

De angst overvalt ons (...) terwijl talrijke fysieke uitingen goed gekarakteriseerd zijn (roerloosheid, sthenocardie, zweten, bevingen...). Maar wat is 'wezen'? Het wezen van de angst is niet te vinden in vaatvernauwing, geremdheid, allemaal verschijnselen die bij angst niet gemist kunnen worden.....

Het wezen van de angst
S. Vestdijk

Manuscript
Anny Le Doux
Omslag, vormgeving en adviezen
Lidwien Steenbrink
Lay-out
Henk Jas
Druk
Ben Meerstad

Paranimfen
Ton van Boxtel
Harald Merckelbach

CONTENTS

DANKWOORD

Een dissertatie is feitelijk een wetenschappelijke verhandeling met een schier onuitputtelijk aantal co-auteurs. Dit proefschrift kwam tot stand dank zij verdraagzaamheid, inlevingsvermogen, nadrukkelijke clemetie en niet-aflatende trouw. Al de collega's van Medische Psychologie, onder leiding van Joost Bremer ben ik dankbaar voor hun voortdurende steun en samenwerking. Ook met de ex-collega's van Geestelijke Gezondheidkunde is de samenwerking steeds bijzonder plezierig geweest. Hieruit is een hechte onderzoeksband met Harald Merckelbach en Anita Jansen gegroeid.

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Anny Le Doux heeft alle papers en de hele tekst van het proefschrift op de haar eigen trefzekere wijze, en met grote nauwgezetheid getypt. Samen met Angela Silanoe-Verweij stond zij voortdurend paraat, om k's in c's te veranderen of anderszins aan een perfectieneurose tegemoet te komen. Isel van Noppen was in de laatste fase de perfecte bliksemafleider voor flitsende zenuwen. De rode pen werd vakkundig gehanteerd door Pamela Falger-Cohen (artikelen) en Marijke van der Horst (hoofdstukken). Zij wisten van mijn Nederlands-Engels ècht Engels te maken. De omslag en de adviezen over de vormgeving van de hand van Lidwien Steenbrink maakten het proefschrift tot een mooi geheel. De steun van Henk Jas bij de uitvoering daarvan was onontbeerlijk.

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De wortels van het onderzoek zijn zeer duidelijk te traceren: een speciaal woord van dank komt dan ook mijn promotor Marcel van den Hout toe. De gedeelde werkplek heeft tot veel gezamenlijke, soms wilde, ideeën en onderzoeksplannetjes geleid. Overigens heeft hij alle ruimte gelaten om het proefschrift te laten worden tot wat het nu is. Onze op sommige punten overeenkomstige en op andere punten geheel tegengestelde werkwijze heeft tot zeer vruchtbare en altijd plezierige samenwerking geleid.

SAMENVATTING

Dit proefschrift bevat een aantal wetenschappelijke studies over agorafobie en paniekstoornis, waarin de relatie tussen hypocapnie en angst centraal staat. Deze onderzoeksverslagen worden voorafgegaan door twee inleidende hoofdstukken om de studies in een breder theoretisch kader te plaatsen. Ze worden gevolgd door een hoofdstuk waarin de belangrijkste bevindingen worden bediscussieerd.

In **hoofdstuk 1** wordt het concept neurotische angst in een historische context geplaatst, worden de basisbegrippen toegelicht, en het differentieel klassiek conditioneringsparadigma - zoals dat in veel experimentele studies wordt gehanteerd - besproken. Tevens volgt een korte samenvatting van de belangrijkste tekortkomingen van klassieke conditionering voor wat betreft de verklaring van neurotische angst. De (fysiologische) toestand waarin het onderzoekssubject zich bevindt, als determinant voor aangeleerde angst, vormt een ernstig hiaat in de bestaande literatuur.

In **hoofdstuk 2** wordt een algemeen kader geschetst waaruit de onderzoeksvragen zijn afgeleid. In het eerste deel van dit hoofdstuk ligt de nadruk op de theoretische overwegingen die tot de onderzoekshypothesen hebben geleid. Het betreft de invloed die het organisme of het subject heeft op het aanleren en instandhouden van angst. Achtereenvolgens worden besproken de leergeschiedenis van het subject, gereflecteerd in persoonlijkheidstrekken en jeugdervaringen, fysiologische variabelen, met de nadruk op respiratoire alkalose, en cognitieve variabelen. Een cognitief-fysiologische benadering

van paniek wordt uiteengezet. In het tweede gedeelte van dit hoofdstuk worden de research-hypothesen samengevat.

Hoofdstuk 3 is een bundeling van experimentele studie die de basis voor dit proefschrift vormen. De invloed van het organisme vormt daarin het centrale thema. De eerste twee studies betreffen de invloed van jeugdervaringen en persoonlijkheidseigenschappen; de studies drie, vier en vijf benadrukken de mogelijke rol van een systemische hypocapnie bij het ontstaan en instandhouden van pathologische angst; en in de laatste studie staan cognitieve factoren centraal.

Hoofdstuk 3.1 behandelt de vraag of separatie angst in de jeugd een predisponerende factor is voor angststoornissen op latere leeftijd. Veelal wordt aangenomen dat zowel vroege scheiding van de ouders, alsook specifiek, scheidingsangst van het kind kan leiden tot agorafobie of paniekstoornis. In een uitgebreide retrospectieve vragenlijststudie werd deze specificiteitshypothese getoetst. Daartoe werden agorafobie patiënten vergeleken met zowel neurotische- als normale controle personen. De resultaten toonden aan dat agorafobie/paniek patiënten vaker dan "normale" gezonde controle personen aan separatie angst hadden geleden en tevens dat zij iets vaker van hun ouders gescheiden waren geweest. Echter, een groep neurotische patiënten zonder klachten van panische of agorafobische aard waren nog vaker van hun ouders gescheiden en hadden nog vaker aan separatie angst geleden. Vroege scheiding van ouders, en separatie angst blijken dus niet specifiek voor de ontwikkeling voor agorafobie of paniek.

Hoofdstuk 3.2 behandelt de relatie tussen agorafobie en "locus-of-control". In de literatuur zijn suggesties te vinden dat agorafobici persoonlijkheidskenmerken vertonen die specifiek met agorafobie zouden samengaan. Omdat interne-externe controle kan functioneren als een moderator variabele tussen ervaren stress en angst, vervult het concept "locus-of-control" mogelijk een sleutelrol in het ontstaan van agorafobie of paniek. Er werd onderzocht of de agorafobie/paniek pati137nten in sterkere mate een externe oriëntering vertonen dan zowel gezonde "normale" vrijwilligers, als een controle groep neurotische patiënten. Deze drie groepen werden vergeleken op hun score op de Nederlandse versie van de Rotter IE-schaal. De resultaten ondersteunden de hypothese niet. Integendeel, terwijl beide neurotische groepen een sterke externe oriëntering laten zien ten opzicht van de "normale" controle personen, vertoonden de agorafobie/paniek patiënten een lagere score (meer intern) dan de neurotische controle groep. Externe oriëntering is veeleer een kenmerk van neurose in het algemeen dan specifiek van agorafobie of paniek. Bevindingen uit zowel hoofdstuk 3.1 als 3.2 maken duidelijk dat het van doorslaggevend belang is om, in-

dien men specifieke kenmerken van bijvoorbeeld paniekpatiënten wil identificeren, de referentiegroep niet alleen te laten bestaan uit "normale" controle personen, maar om ook gegevens van andere psychiatrische patiënten als vergelijkingsmateriaal in de beschouwing te betrekken. De huidige resultaten dragen niet bij tot de klinische claim dat agorafobici zich door specifieke persoonlijkheidskenmerken van anderen zouden onderscheiden.

In *hoofdstuk 3.3* wordt de scheve verdeling van angsten over de sexen toegelicht. In de hier beschreven studie werd getoetst of veranderingen inherent aan de menstruele cyclus, en dan met name de pre-menstruele fase, vrouwen kwetsbaar maken voor angst. Twee groepen vrouwen, de ene groep in haar pre-menstruele periode en de andere elders in haar cyclus, werden met elkaar vergeleken in een conditioneringsstudie. De hypothese luidt dat de "pre-menstruele" vrouwen een geconditioneerde electrodermale response sneller zullen aanleren en dat zij een vertraagde extinctie van die responsen zullen vertonen. De hypothese werd gedeeltelijk bevestigd. De acquisitie was inderdaad gefaciliteerd. Ook tijdens extinctie verschilde de "pre-menstruele" van de controle groep. Dit verschil kan echter vermoedelijk worden toegeschreven aan de verschillen die tijdens de acquisitie zijn ontstaan zodat de kwestie van vertraagde extinctie vooralsnog onopgelost blijft. In de speculatie over het mogelijk onderliggende mechanisme wordt de premenstruele relatieve hypocapnie betrokken. De relatie tussen (respiratoire) alkalose en angst, en hypocapnie als mogelijk verantwoordelijk mechanisme voor de verhoogde kwetsbaarheid voor het aanleren van angst, is onderwerp van verdere studie.

Een nadere toelichting op de relatie tussen hypocapnie en angst wordt gepresenteerd in *hoofdstuk 3.4.* Twee groepen gezonde, normale vrijwilligers ondergingen lactaat- en placebo infusies. Beide groepen, de ene verwachtte "plezierige opwinding" en de andere verwachtte negatief affect, vertoonden een voorspelde, significante afname in pCO_2 na lactaat. Deze hypocapnie ging vergezeld van een afname in ademfrequentie in de proefpersonen die angstig werden, in een toename in ademfre- quentie in de niet-angstige groep. De pCO_2 daling in de angstige groep was significant groter dan in de andere groep.

In *hoofdstuk 3.5* worden twee experimenten beschreven waarin de invloed van hypocapnie op het ontwikkelen van angst nader wordt bestudeerd. De nauwe verwantschap tussen alkalose en angst heeft geleid tot de veronderstelling dat de alkalose op zich de acquisitie van stimulus-gebonden angst faciliteert en/of de extinctie ervan inhibeert. In experiment I wordt de hypothese getoetst dat de acquisitie van een geconditioneerde electrodermale response wordt gefaciliteerd en dat de daaropvolgende extinctie van de responsen wordt geïnhibeerd, indien de proefpersonen zich tijdens de acquisitie in een

toestand van hypocapnie bevinden (en in een toestand normocapnie tijdens de extinctie). In experiment II wordt de hypothese getoetst dat de extinctie van geconditioneerde electrodermale responsen (aangeleerd tijdens normocapnie) geïnhibeerd is, indien de proefpersonen zich tijdens de extinctie in een hypocapnische toestand bevinden. Alle deelnemers konden een hypocapnie verdragen zonder daarbij angstig te worden. Op die wijze was het mogelijk de effecten van de hypocapnie als zodanig te scheiden van de subjectieve interpretatie van de lichamelijke sensaties die door de hypocapnie teweeg worden gebracht. Geen van de hypothesen kon worden bevestigd. De resultaten van deze experimenten tonen aan dat de geïnduceerde fysiologische veranderingen op zich geen voldoende voorwaarde zijn voor een verhoogde kwetsbaarheid voor het aanleren of instandhouden van angst. De interpretatie van de lichamelijke sensaties die door de respiratoire alkalose worden geïnduceerd kunnen een interessante alternatieve verklaring vormen.

In *hoofdstuk 3.6* wordt de invloed van cognitieve factoren nader uitgewerkt. In een dubbel-blinde placebo gecontroleerde, studie kregen twee verschilllend geïnstrueerde groepen vrijwilligers lactaat en placebo toegediend op twee verschillende dagen. Het bleek mogelijk om angst te induceren in overigens niet angstige personen. Dit effect werd teweeggebracht door de cognitieve set van de deelnemers zodanig te manipuleren dat zij de lactaat infusies als angstopwekkend ervoeren. Bij deze studie springen twee zaken in het oog. De aanwezigheid van fysieke symptomen is van cruciaal belang voor het optreden van angst: wanneer een placebo werd gegeven vertoonden de personen in de ene, noch in de andere groep enige veranderingen in emotie. De instructie alleen was dus niet voldoende. Indien echter relevante instructies werden gegeven in aanwezigheid van fysieke verschijnselen, dan werden de betreffende personen zeer angstig.

Tot slot worden in **hoofdstuk 4** de onderzoeksbevindingen samengevat en bediscussieerd, waaruit implicaties voor verder onderzoek volgen. Uit het gepresenteerde onderzoek wordt steun gevonden voor een cognitief-fysiologische benadering van paniek. Een systemische alkalose als zodanig is niet voldoende voorwaarde voor het aanleren van angst. Evenmin geldt dat voor een negatieve cognitieve set alleen. De combinatie van fysiologische sensaties en anxiogene interpretatie van die sensaties vormt waarschijnlijk een belangrijke determinant van het soort neurotische angst waaraan paniekpatiënten en agorafobici lijden.

SUMMARY

In this dissertation a number of research papers on agoraphobia and panic disorder are presented, with the main focus on the relationship between hypocapnia and anxiety. These papers are preceded by two introductory chapters which place these studies within the broader context of existing literature. The research papers are followed by a concluding chapter in which the research findings are discussed.

In **chapter 1** the concept of anxiety neurosis is placed in a historical perspective, the basic concepts are discussed, and the differential classical conditioning paradigm - as used in many experimental studies on anxiety - is introduced. The shortcomings of the classical conditioning paradigm in the understanding of anxiety are briefly summarized. Knowledge about the role of the state of the organism in the acquisition of panic forms an important gap in existing literature.

In **chapter 2** the general perspective from which the research questions were derived, is introduced. In the first part of this chapter, theoretical considerations are presented concerning the influence of the organism on the acquisition and maintenance of anxiety. Learning history, as reflected in personality traits and childhood experiences; physiological variables, with the emphasis on respiratory alkalosis; and cognitive variables are discussed subsequently. A cognitive-physiological approach to panic is presented. In the second part of this chapter the research hypotheses are summarized.

Chapter 3 deals with the experimental studies that were carried out. The influence of

the organism, with the emphasis on organismic variables in general and systemic alkalosis in particular, on the acquisition and maintenance of panic, is the central theme. The first and second studies concern the influence of childhood experiences and of personality traits; the studies three, four and five stress the possible role of systemic alkalosis, and in the final study cognitive factors are emphasized.

Chapter 3.1 deals with the question of childhood separation anxiety as a precursor to adult anxiety disorders. It is often suggested that both early parental separation and childhood separation anxiety specifically predispose people to adult agoraphobia or panic disorder. In an extensive retrospective self-report study this specificity hypothesis was tested. Agoraphobic and panic disorder patients were compared with both neurotic controls and normal controls. It was found that agoraphobic/panic patients had suffered more from separation anxiety in their youth or childhood than a normal control group had and also that they had been separated from their parents somewhat more often. However, early separation and separation anxiety turned out not to be specific for agoraphobia or panic disorder. A control group of non-panicking neurotic patients, had suffered even more from separation anxiety.

Chapter 3.2 describes the relationship between agoraphobia and "locus-of-control". In literature it is suggested that agoraphobics do have unusual personalities but that they may have had normal personalities before their agoraphobia began. Because internal-external control can act as a moderator variable between life stress and anxiety, the "locus-of-control" concept is important to consider. It was hypothesized that agoraphobic/panic patients are more externally oriented than both normal controls and non-agoraphobic neurotic controls. The scores of these three groups on the Dutch version of the Rotter IE-scale were compared. The data did not support the hypothesis. On the contrary, while both neurotic samples displayed a more external orientation than the normal control group did, agoraphobic/panic patients tended to score somewhat lower on the IE-scale than the neurotic controls did. It appears that an external locus-of-control is characteristic of neurosis in general rather than of agoraphobia in particular. The results of this study do not add to the clinical claim that agoraphobics are distinguished from others by specific personality characteristics. The findings from chapters 3.1 and 3.2 highlight the desirability of an appropriate reference group when an attempt is made to describe specific features of agoraphobic/panic disorder patients.

In *chapter 3.3* the skewed sex-distribution of anxiety disorders is discussed. The study described in this chapter was based on the proposition that changes inherent in the men-

strual cycle, and in the premenstrual phase in particular, may predispose women to negative affect. Two groups of women were compared in a conditioning study. One group in their pre-menstrual phases and the other one anywhere in their cycles. It was hypothesized that the 'pre-menstrual' women would show an enhanced susceptibility to the acquisition of a conditioned skin conductance response and to delayed extinction, when compared with women at other points in their cycles. The results of the study partly confirmed the hypothesis. The acquisition of a conditioned response was, indeed, facilitated in the premenstrual group. During extinction too a difference emerged between the two groups. However, this difference in extinction can probably be explained by the mere fact that premenstrual women readily acquired the conditioned response while control women did not. So the question of delayed extinction is still open. In speculating about the underlying mechanism that facilitates the acquisition of fear, the relative premenstrual hypocapnia is considered. The relationship between (respiratory) alkalosis and anxiety, and the possible role of alkalosis as a mechanism responsible for the enhanced acquisition of fear is the subject of the studies discussed below.

A further illustration of the relationship between hypocapnia and anxiety is found in *chapter 3.4.* Two groups of healthy normal volunteers were subjected to placebo and lactate infusions. Both groups, one of which expected pleasant excitement, and one of which expected anxious affect, showed an expected, significant decrease in alveolar pCO_2 after lactate. This was accompanied by an increase in respiration rate in those subjects who became anxious and a decrease in those who didn't. The decrease in pCO_2 was significantly greater in the anxious group as compared to that in the other group.

In *chapter 3.5* two experiments are described in which the influence of hypocapnia and respiratory alkalosis on the development and maintenance of fear responses was investigated. The very close relationship between alkalosis and anxiety has led to the hypothesis that the alkalosis in itself facilitates the acquisition of stimulusbound anxiety and/or inhibits the extinction of acquired anxiety. Experiment I tested the hypothesis that the acquisition of conditioned galvanic skin responses is facilitated and that the subsequent extinction of these responses is inhibited, when subjects are in a state of hypocapnia during the acquisition (and normocapnic during extinction). Experiment II tested the hypothesis that the extinction of conditioned galvanic skin responses (acquired in a state of normocapnia) is delayed, when subjects are in a state of hypocapnia during the extinction. All participating subjects could tolerate a hypocapnia without getting anxious. Thus we were able to separate the effects of the respiratory alkalosis as such, from the subjective interpretation of

the symptoms caused by the alkalosis. None of the hypotheses were confirmed, however. Data from these studies show that physiological changes per se do not constitute a sufficient condition to enhance the acquisition and maintenance of neurotic fears. The interpretation of the sensations induced by the alkalosis may offer an alternative explanation.

In *chapter 3.6* these cognitive aspects of panic are further elucidated. In a double-blind placebo-controlled cross-over study, two differently instructed groups received placebo and lactate on two different days. It was possible to induce experimental panic in normal subjects. This was brought about by manipulating the cognitive set in such a way that subjects interpreted the sensations induced by lactate as anxiety provoking. By the results of this study two points are stressed. The presence of physical symptoms is of crucial importance for the existence of anxiety: when a placebo was given subjects neither in the anxious group nor in the other group showed any mood changes. So, the instruction alone was not able to induce any mood changes. But, even more important, just by giving the relevant suggestions in the presence of certain bodily sensations to this healthy group of people, they became highly anxious. They felt as anxious as normally only panic patients do. These data are discussed in the context of a cognitive-physiological model of anxiety.

Finally in **chapter 4**, the research findings are summarized and discussed. Support is found for the cognitive-physiological approach to panic. An alkalosis as such is not a sufficient condition for a facilitated acquisition of neurotic fears, neither is a negative cognitive set alone. The combination of physical sensations and anxiogenous interpretation is an important determinative factor in the maintenance of panic.

CHAPTER ONE

PHENOMENOLOGY AND CLASSIFICATION OF ANXIETY DISORDERS

1.1
Introduction

Anxiety is one of the most disabling symptoms recognized in psychiatric practice. Although anxiety may be considered a normal and adaptive response to environmental stress, whenever it bears little relationship to the stressor, is unrelenting, or restricts normal functioning, it is referred to as pathological anxiety. Only a small fraction of the people suffering from anxiety disorders seek help of any kind. Epidemiological studies report a community prevalence of 2.9-8.4 percent (Marks, 1986). Risk factors include young age, female gender and familial history (Weissman & Merikangas, 1986). One of the appearances of pathological anxiety, non-situational panic, was the main focus of this study.

Clinicians and researchers recognize the importance of a common language in which they can communicate about different disorders. An important diagnostic tool using reliable operational criteria, is found in the third edition of the "Diagnostic and Statistical Manual of Mental Disorders" of the American Psychiatric Association, commonly known as DSM-III (APA, 1980). One of the categories is composed of the anxiety disorders: phobic disorders (or phobic neurosis), anxiety states (or anxiety neurosis), post-traumatic stress disorder, and atypical anxiety disorder. The essential feature of phobic disorders is

(DSM-III)

...persistent and irrational fear of a specific object, activity or situation that results in a compelling desire to avoid the dreaded object, activity or situation (the phobic stimulus). .. when the avoidance behaviour is a significant source of distress to the individual or interferes with social or role functioning, a diagnosis of phobic disorder is warranted.

The phobic disorders are subdivided into: agoraphobia (with or without panic attacks), social phobia, and simple phobia. In the anxiety states three subtypes are described: panic disorder, generalised anxiety disorder and obsessive compulsive disorder (or obsessive compulsive neurosis).

Panic disorder is defined as (DSM-III)

...recurrent panic attacks that occur at unpredictable times, ... in circumstances other then during marked physical exertion or in a life threatening situation.

Panic attacks are characterized by discrete periods of apprehension or fear and during each attack at least four of the following symptoms appear: (1) dyspnea, (2) palpitations, (3) chest pain or discomfort, (4) choking or smothering sensations, (5) dizziness, vertigo, or unsteady feelings, (6) feelings of unreality, (7) paresthesias (tingling in hands or feet), (8) hot and cold flashes, (9) sweating, (10) faintness, (11) trembling or shaking, (12) fear of dying, going crazy, or doing something uncontrolled during an attack.

Panic disorder and agoraphobia may be closely related disorders. Some agoraphobic patients describe panic attacks that occur in non-phobic situations (Roberts, 1964) and many report the development of agoraphobic fears following the onset of periods of seemingly spontaneous panic attacks (Mendel & Klein, 1969; Sheehan et al., 1980). On the other hand, many patients treated for panic disorder show a certain degree of agoraphobic avoidance. Recent investigations support the view that agoraphobia could be a complication of panic disorder. (Thyer & Himle, 1985). In an extensive study of patients who met DSM-III criteria for panic disorder and patients with agoraphobia with panic attacks, demographic, psychometric, and clinical features were compared (Thyer et al., 1985). The researchers could not demonstrate any significant differences between the two groups. Furthermore, the histogram plottings of the ages of onset of both disorders in the work of Sheehan et al. (1981) appear virtually identical. The above data seem to support the view that panic disorder and agoraphobia with panic attacks both belong to the same class of anxiety neurosis. This conviction is indeed incorporated in the DSM-III-R, the revised version of the DSM-III (APA, 1988).

1.2
Anxiety disorder in a historical perspective

Panic disorder and agoraphobia with panic attacks appear for the first time in the Diagnostic and Statistical Manual in 1980. That does not mean, however, that these disorders did not exist before. On the contrary, they have been known throughout medical history under a wide variety of diagnostic labels, seemingly referring to the same symptoms. As early as 1872, Westphal described patients with complaints strikingly similar to DSM-III agoraphobia with panic attacks:

Er beklagt sich, das es ihm unmöglich sei über freie Plätze zu gehen. Es überfällt ihm bei dem Versuche dazu sofort ein Angstgefühl, dessen Sitz er auf befragen mehr im Kopfe als in der Herz gegend angiebt, indem sei auch Herzklopfen dabei (...) und damit verbindet sich das erwähnte, oft von allgemeinem Zittern begleitete Angstgefühl (p.139).

Westphal was, in fact, the first one to introduce the word agoraphobia:

Diese Furcht vor dem Durchschreiten von Plätzen resp. Strassen stellte derart das Hauptphänomen dar, das ich, obwohl (...) nicht ganz erschöpfend, das Wort Agoraphobie, Platzfurcht, dafür bilden zu können meinte (p.138).

According to Errera (1962) it may be possible to trace phobia as far back as to the early writings of Celsus (1814), Le Camus (1769), Aurelianus (1722), or even Hippocrates, but more often Westphal's classical work "Die Agoraphobie" (1872) is accepted as the starting point for literature on agoraphobia. A year before, DaCosta (1871) described the "irritable heart", a functional disorder of the heart found mostly among soldiers but also recognized in civilian populations.

I propose to consider a form of cardiac malady common among soldiers, but the study of which is equally interesting to the civil practitioner as account of its intimate bearing on some obscure or doubtful points of pathology.

During the Civil War, DaCosta observed numerous soldiers suffering from this mysterious malady which completely incapacitated them for duty. The symptomatology would almost have met the DSM-III criteria for anxiety neurosis except for the fact that chest pain, and not anxiety, was most frequently the major complaint. The symptoms consisted of palpitations and difficult breathing, dizziness, nausea, and chest pain. The attacks sometimes lasted for hours and were accompanied by feelings of distress. This complex of symptoms was by subsequent writers referred to as the "DaCosta-Syndrome".

During World War I, Lewis (1918, 1933) described the "effort syndrome" in soldiers,

and again the main symptoms were of a cardiovascular nature. This time, however, the major complaint was a marked fatigue. Lewis (1918) was very explicit in not equating the terms "irritable heart" or "soldier's heart" with "effort syndrome":

...for the reason that they cover the meaning of a primary cardiac disorder (p.5).

Lewis pointed out that the symptoms his patients exhibited were the same as those exhibited by healthy subjects engaged in strenuous exercise, when certain symptoms and physical signs are evoked. The only difference appears to lie in the ease with which the symptoms are elicited, *..though in patients additional symptoms may appear.* (Lewis, 1933, p.158). In later writings, the same clinical condition is indicated by an enormous variety of terms, such as, "cardiac neurosis", "vasomotor neurosis", "neurocirculatory asthenia", "nervous exhaustion", and the like. Freud, however, was the first to introduce the label "anxiety neurosis".

After World War II it has become clear that hyperventilation can cause a series of physical symptoms that resemble the symptoms of the effort syndrome, and some authors point to the striking similarities between the hyperventilation syndrome and anxiety neurosis (Magarian, 1982; Lum, 1981; Garssen et al., 1983; Clark et al., 1985). There are reasons to assume that excessive hyperventilation occurs during panic attacks and that chronic or periodic overbreathing may constitute an important maintaining mechanism. Whereas some authors maintain that hyperventilation is a relatively important aspect of panic disorder (e.g. Clark et al. 1985), others regard the "Hyperventilation Syndrome" as a separate clinical entity (e.g. Lum, 1976). Whether hyperventilation is the explanation of panic disorder or whether hyperventilation is one of the many physiological concomitants of neurotic anxiety is still a much debated, yet unresolved, issue in psychopathology.

As was outlined above, the syndromes which are nowadays known as panic disorder and agoraphobia may be closely related disorders. And now, in 1988, panic disorder is emphasized even more in the revised version of the Diagnostic and Statistical Manual, DSM-III-R. Panic disorder and agoraphobia are lumped together in two categories: panic disorder with, or without agoraphobia, and agoraphobia without a history of panic disorder.

Summarizing, I would like to join Wooley, who concluded in 1976 that he had had to learn from history that

..patient complaints, signs and symptoms are little changed, only the interpretation has changed. The patients are the same, the doctor's understanding improves. (p. 750).

1.3
Conditioning models of anxiety

1.3.1 Classical conditioning

A basic form of learning is classical conditioning, the study of which began with the work of Pavlov. The conditioning of fear is mostly studied by means of rats or dogs and typically involves a neutral stimulus such as a light or a tone that, on first presentation, does not elicit fear. After pairing this stimulus with a second stimulus, that naturally elicits fear reactions, the previous neutral stimulus acquires fear eliciting properties. The previous neutral stimulus was called the condition*al* stimulus, CS, (erroneously translated to condition*ed* stimulus), the aversive stimulus was called the unconditional stimulus, US. The fear reactions following these stimuli were referred to as the unconditional and conditional response, abbreviated as UR and CR respectively.

When classical learning processes are studied in an experimental setting, seemingly trivial changes in US-CS pairings can have profound effects on the latency and magnitude of the responses observed. The optimal procedure for the conditioning of fear reactions is accomplished with "short-delayed" and "trace" conditioning in which the CS is presented shortly before the US. If learning takes place one cannot be sure that it results from the association of CS and US. Therefore control procedures are introduced. An often used, and probably the most sophisticated control procedure, is the differential paradigm, which typically involves two stimuli, one of which is paired with the US (the CS^+) and the other one (the CS^-) is never followed by the US. The procedure consists of three phases: habituation, acquisition and extinction. During habituation both the CS^- and the to-be CS^+ are presented without US, to control for orienting responses. In the acquisition phase, new responses are learned by pairing US and CS^+. During extinction both the CS^+ and CS^- are repeatedly presented without any association with the US and the newly learned behaviour is lost. In animal studies, fear is usually measured indirectly by noting changes in ongoing behaviour, such as freezing. In human conditioning experiments, skin conductance response (SCR) is widely used as a measure for the CR.

1.3.2 The two factor model

Concerning the explanation of naturally occurring anxiety, learning theories have enjoyed considerable prominence. By far the most influential account of phobias is Mowrer's two factor model (Mowrer, 1960). The two factors refer to two forms of learning that are

involved. According to this model, anxieties are acquired by the process of classical conditioning in the first stage. In the second stage, responses that decrease or terminate discomfort arising from the fear eliciting stimulus are learned by the process of operant conditioning. The performance of these responses is reinforced by the subsequent anxiety reduction. Thus, phobias are persistent because such avoidance responses prevent exposure to the feared stimuli and no extinction will occur. Although this model has been very useful, it leaves some central clinical observations unexplained. Dissimilarities between naturally occurring fear and fear in the laboratory have led to criticism of the model.

1.3.3 Limitations of the model

A difficulty in explaining naturally occurring phobic anxiety on the basis of this laboratory model lies in the extinction phenomenon. In laboratory settings extinction of the conditioned response will occur in the absence of the US. Clinical phobias, however, are highly resistant to extinction and even increases of fear can be noted in the absence of any US. A second problem concerns the acquisition of anxiety responses. In a laboratory, several US-CS pairings are needed, whereas natural phobias are often acquired by one-trial learning or, just the opposite, there sometimes is no conditioning history. Furthermore, the Pavlovian "law of equipotentiality", stating that the choice of a CS is a matter of indifference, and the "equivalence of associability", predicting that the nature of the US and CS is not essential in the association processes, do not seem to apply to natural phobias. They comprise a seemingly non-arbitrary and limited set of stimuli. Small animal phobias are far the most common (Agras et al., 1969), while pajama phobias are hardly ever encountered (Seligman, 1971).

Failure to extinguish and increases in fear

To account for an increase in fear responses in a period when extinction would be expected to occur, Eysenck developed the incubation theory of anxiety/fear responses (Eysenck, 1968). This theory states that in some cases the CR can be aversive in itself. The aversive properties of the CR can act as a US and conditioning continues in the absence of the original US. This account seems highly plausible concerning the explanation of non-situational panic or fear-of-fear (Evans, 1972). Experimental evidence to confirm the notion of incubation is sparse however.

Preparedness and belongingness

To account for it that phobias are highly resistant to extinction, comprise a limited set of objects, are rapidly learned, and of a non-cognitive nature, Seligman proposed to extend learning theory with the concept of preparedness (Seligman, 1970). The preparedness hypothesis states that there is a genetically based, "prepared" tendency to associate fear with certain objects, the fear of which is supposed to be of vital importance to the human species' chances of survival.

A large amount of research has been devoted to the quality of the CS. Indeed some clinical evidence for the preparedness hypothesis is found in the studies by DeSilva et al. (1977) and by Zafiropoulou & McPherson (1986). They demonstrated that most simple phobias pertain to objects significant in an evolutionary sense. Most impressive is the extensive experimental work of Öhman and colleagues. In a differential classical conditioning paradigm it was repeatedly found that SCR to pictures of snakes and spiders extinguishes more slowly than that to flowers or mushrooms (Öhman et al., 1976; Öhman, 1986). All attempts to replicate this effect outside Öhman's research group, however, yielded disappointing results (Merckelbach, van der Molen & van den Hout, 1986; for review see: McNally, 1987).

Seligman & Hager (1972) explicitly stress that it is not only the quality of the CS that is involved, but rather that certain associations are more likely to be made than others. It has indeed been recognized that rats are willing to associate taste with illness but not with shock (Garcia & Koelling, 1966). Shocks do not "belong with" taste. The interaction between the nature of the US and the nature of the CS has been studied extensively in this "conditioned taste aversion" (CTA) paradigm. However, from a very profound and extensive review of CTA, Klosterhalfen & Klosterhalfen (1985) had to conclude that

...Seligman's (1970) speculation (..) receives little support from our comparison of learning phenomena in CTA and traditional learning...

For the moment it seems undecided whether the preparedness hypothesis is a valuable extension of the classical conditioning model for phobias.

Awareness and volition

Work on animal conditioning has been of major significance in the development of the understanding of human neurotic disorders. An excellent review of animal models of phobias, obsessive-compulsive reactions and generalized anxiety, was recently presented by Mineka (1985). These models illuminate similarities in etiology of animal and human

neurotic disorders, and give suggestions for therapeutical applications (Wolpe, 1958). However, a complicating factor is that human subjects fail to acquire long-lasting fearreactions in a laboratory, although theory predicts their occurrence (Rachman, 1977). Furthermore, human subjects are distinguished from animal subjects by awareness and volition. So, in experimental human conditioning the problem arises that subjects might voluntarily control the reaction that is to be conditioned: the law of conditioning does seemingly not extend to voluntary responses (Coleman, 1985). The complicating factor of awareness is highlighted even more, when the influence of instruction is considered. An immediate reversal of conditioned electrodermal response curves can be obtained, if subjects, after discrimination training, are informed that the CS-US contingencies are reversed (McNally, 1981). Rachman (1977) proposes to regard two indirect pathways to fear beside fear-acquisition by conditioning (including prepared learning and CTA). He suggests that both vicarious acquisition, and fear acquisition by transmission of information and/or instruction may be of significance.

The above suggests that in human experiments, cognitive and instructional variables should be accounted for, when studying fear acquisition processes. More precisely, very important factors to consider are intra-subject variables that can influence the etiology or maintenance of anxiety responses. Intra-subject variables may be the cognitive and/or physiological state of the organism. These intra-subject factors will constitute the primary focus of our experimental work. A series of hypotheses concerning cognitive, instructional and physiological variables are derived from literature and will be tested experimentally.

CHAPTER TWO

INTRA-SUBJECT DETERMINANTS OF ANXIETY

STATEMENT OF THE PROBLEM

2.1
Theoretical considerations

In a learning theoretical approach to anxiety, the importance of factors within the organism is appreciated more and more nowadays. Behaviour (R) is not only determined by the stimulus (S) but also by variables within the organism (O). A shift from an S-R toward an S-O-R paradigm can be noted. In the organism both physiological and cognitive factors can play an important role in the acquisition and maintenance of anxiety. These two aspects formed the focus of our research. The differential classical conditioning paradigm, as described in chapter 1.2, was used for studying the relationship between physiological changes, and the acquisition and extinction of anxiety. Besides this learning history was considered.

2.1.1 Learning history

Childhood experiences

There is little question as to whether early separation may be considered as a highly traumatic event: the availability of attachment figures is often stressed (Bolwby, 1973). Several authors maintain that early parental separation and more specifically childhood separation anxiety are associated with the development of adult agoraphobia and panic disorder. This conviction was incorporated in DSM-III and still is in DSM-III-R. The symptom similarity between these syndromes is indeed striking. But, this incorporation is probably mainly based on the influential work of D.F. Klein and associates. In his biological approach to panic disorder and agoraphobia with panic attacks, a specific biological vulnerability in Central Nerve System is postulated (Klein, 1981). The model is based on the observation that panic attacks can be treated effectively with the antidepressant imipramine but the background anxiety cannot (Klein, 1964; Klein & Fink, 1962). It is also claimed that school phobia, too, can be treated with imipramine (Gittelman-Klein & Klein, 1971). This has led to the etiological consideration that school phobia predisposes people to agoraphobia or panic in adulthood. Nevertheless, data on separation anxiety as a precursor to APD mainly stem from uncontrolled observations and clinical impressions (Klein, 1964; Gittelman-Klein, 1975; Gittelman-Klein & Klein, 1973; 1985). Up till now there are at least two empirical failures to confirm this hypothesis (Thyrer et al., 1985; 1986). Concerning the drug specificity, Marks (1983) also came to a negative conclusion in a meta-analysis of 19 controlled drug treatment studies. Thus, empirical evidence is far from unequivocal. (chapter 3.1)

An agoraphobic personality?

The second problem is that agoraphobia seems to manifest itself as a sexspecific symptomatology (Weissman, et al., 1986). Female agoraphobics have been described as behaving "superfeminine" (Fodor, 1974). This is one of the reasons why specific personality traits have been assumed to predispose people to agoraphobia. In clinical observations, agoraphobics have indeed been characterized as timid, shy and unassertive, dependent and socially anxious, immature, depressed, and the like (see: Marks, 1969). However, without a reference group these observations are hard to interpret. When empirical studies employing a variety of control groups are reviewed, this picture is less clear. In a study of the outcome of a therapy employing assertive training for female agoraphobics, Haimo & Blit-

man (1985) concluded that these women had a "deficit" of "masculine" traits, rather than a surplus of feminine ones. Mavissakalian (1985), did not find differences in the personality dimensions of extraversion, introversion or assertiveness between male and female agoraphobics, but no reference was made to other control groups. Low levels of self-sufficiency, more field dependency and less assertiveness have been reported for agoraphobics as compared to simple phobics (see: Chambless, 1982). In their extensive review of agoraphobic characteristics, Foa et al. (1984) came to the conclusion that the theory of the "dependent personality" has gained support, albeit that methodological weaknesses occur. In a carefully controlled and methodologically sound design Arrindell and Emmelkamp (1987) did not find any support for the hypothesis that agoraphobics are more dependent than controls. On the other hand, the agoraphobics could be distinguished according to neuroticism, seclusion, passivity and intropunitiveness.

Summarizing, it can be stated that the picture arising from literature is that phobic patients seen in a clinic may have unusual personalities. But one has to bear in mind that they may have had "normal" personalities before their phobia began. Why, then, did these subjects develop anxiety disorder? Johnson & Sarason (1978) demonstrated that internal-external control can act as a moderator variable between life stress and anxiety. Therefore an important personality factor to consider is "locus-of-control" (Rotter, 1954; Rotter et al., 1962). It has indeed been demonstrated that external orientation, as measured with Rotter's IE-scale, is related to agoraphobia (Emmelkamp & Cohen-Kettenis, 1975; Adler & Price, 1985; Hoehn-Saric & McLeod, 1986). This concept may, however, be nonspecific since it is not clear whether external orientation is also associated with other diagnostic groups. The question of specificity of the locus-of-control concept to agoraphobia is subjected to experimental verification (chapter 3.2).

2.1.2 Physiological variables

Sex differences

As we have seen in the previous paragraph, the sex distribution of anxiety disorders, particularly that of agoraphobia is skewed (Emmelkamp, 1982). About two thirds to three quarters are female, a reason why agoraphobia is often referred to as a "housewives' syndrome". Some authors explain this sex difference by the social position that women have (Bekker, 1986) or as a form of cultural disposition (De Swaan, 1979), but when a closer look is taken at the literature on women and anxiety, the relationship between anxiety and

menstrual cycle becomes obvious. Most data stem from studies on women suffering from the "pre-menstrual syndrome" (PMS). These studies have been severely criticized for methodological (Slade, 1984; Rubinov & Roy-Byrne, 1984; Halbreich & Endicott, 1985) and sociocultural reasons (Ruble & Brooks-Gunn, 1979). However, in some controlled blind or prospective studies, changes in anxiety level are still found (e.g. Wilcoxon et al., 1976; Rubinov et al., 1984; May, 1975). Of great interest is a recent study by Cameron et al. (1987). Eight female patients with agoraphobia or panic disorder rated blind, prospectively a number of anxiety and depressive symptoms. They also rated these symptoms retrospectively at the end of the prospective study. Retrospective ratings fluctuated significantly across the menstrual cycles, and the pre-menstrual ratings were highest. The prospective results, however, did not show any consistent pictures of fluctuation. The researchers (Cameron et al., 1987) concluded that

...women with panic attacks do not have premenstrual anxiety increases, but might have increases in other symptoms which they tend to recall as increases in anxiety severity.

A biological basis for the PMS is finding support in studies reporting a series of pre-menstrual somatic changes that are not under volitional control (Wilcoxon et al., 1976; Damas-Mora et al., 1980; Kuczmierzyck & Adams, 1986; Asso, 1986).

The proposition that physiological changes inherent in the menstrual cycle, and in the pre-menstrual phase in particular, may predispose women to negative affect, was the starting point of an empirical investigation and did indeed gain support from the experimental data (chapter 3.3).

Alkalosis and anxiety

The intriguing question remains, what underlying mechanism facilitates acquisition of fear and inhibits its extinction during the pre-menstrual phase. In literature on the PMS reference is hardly ever made to experimental anxiety research and vice versa. However, literature on experimental panic provocation and on hyperventilation provide some interesting suggestions. Systemic alkalosis seems to play an important role in the genesis and maintenance of anxiety neurosis and may provide a link between anxiety on the one hand and the skewed sex distribution and the menstrual cycle on the other hand.

First, it is known from literature on the hyperventilation syndrome (HVS) that the symptoms constituting the HVS are very similar to those of panic disorder: intense anxiety is common in the HVS, and profound hyperventilation (HV) plays a role in maintenance of complaints in approximately 66% of agoraphobic patients (Garssen et al., 1983). HV

induces a lowering of pCO_2 and symptoms characteristic of the HVS are, at least partly, the result of this respiratory alkalosis (Gelder, 1986; Lum, 1981; Magarian, 1982; Garssen et al., 1983; Garssen, 1986). There is empirical evidence that HV can elicit full-blown panic attacks and that chronic or periodic overbreathing can be considered as an important mechanism for the maintenance of panic (Lum, 1976; Hibbert, 1984; Ley, 1985; Clark et al., 1985; Salkovskis & Clark, 1986).

Second, a similar phenomenon occurs in experimental panic provocation interventions, such as lactate infusions. Since 1967, the time that Pitts and McClure, with their nowadays almost famous experiments, demonstrated the anxiogenic properties of lactate infusions, the lactate infusion as an experimental model for panic has proved its validity. The infusion induces a number of physical symptoms typical of anxiety, such as palpitations, dyspnea, dizziness, etc. Panic patients react to these interventions with extreme anxiety and normals do not. It is clear, however, that an elevated serum lactate is neither sufficient nor necessary for the occurrence of pathological anxiety. In a theoretical consideration, and at the same time a very critical attack on Pitts and McClure, Grosz and Farmer (1969) argued that it is not the lactate that is responsible for the panic symptoms, but rather the alkalosis caused by the lactate. In a subsequent experimental study with normal, healthy volunteers this could indeed been demonstrated by the use of a bicarbonate infusion that directly effects the acid-base balance (Grosz & Farmer, 1972).

Third, a fair amount of research has also been carried out on the relationship between the effects of the inhalation of a 35%CO_2-65%O_2 mixture and panic. A single, vital-capacity inhalation of this mixture reliably induces physical symptoms comparable to those of lactate infusions or of HV provocation and also elicits high anxiety in panic patients (Griez et al., 1987; Fyer et al., 1987). Somewhat paradoxically, this anxiety is evoked by the hypocapnia following an initial hypercapnia. The immediate effect of carbondioxide inhalation is an acidosis, but because of the very strong stimulation of the chemoreceptor system, the CO_2-inhalation is followed by hyperventilation, resulting in an alkalotic "overshoot" (Van den Hout & Griez, 1985).

Furthermore, it is not unlikely and theoretically plausible that respiratory alkalosis also exists in clinical panic. For practical reasons research about that is hard to perform: panic attacks seldom show up spontaneously in a laboratory. Griez et al. (1987), however, were in the lucky circumstance to observe a natural panic in the laboratory. Immediate blood gas analyses showed a depressed pCO_2 and elevated pH. With the aid of a 24-hours ambulatory monitoring technique Hibbert (1984) demonstrated that the self-reported pa-

nics are accompanied by an alakalosis, albeit a relative one. Interesting, too, is the case study of Salkovskis (Salkovskis et al., 1986). It concerns a patient on renal dialysis showing substantially larger changes in pCO_2 and blood pH when he panicked, than on other occasions.

Finally, an observation from one of our studies should not be left unmentioned here. Two groups healthy normal volunteers showed an expected, significant decrease in alveolar pCO_2 after lactate. This was accompanied by an increase in the respiration rate of those subjects who became anxious and a decrease in the respiration rate of those who did not. The decrease in pCO_2 was significantly greater in the anxious group as compared to that in the other (chapter 3.4).

To sum up, literature on carbondioxide inhalations, the hyperventilation syndrome, and clinical and experimental observations, point to a systemic alkalosis as a final common pathway to panic.

These findings may be related to the menstrual cycle by considering that during the pre-menstrual phase, pCO_2 tends to be relatively low (Damas-Mora et al., 1980). Thus, the pre-menstruum may be relevant for the etiology of anxiety disorders since, during this phase, women are likely to be hypocapnic. It can be hypothesized that this pre-menstrual hypocapnia interacts with conditioning processes. A lowered pCO_2 may, in itself, facilitate acquisition and inhibit extinction of fear responses. Kartsounis and Turpin (1987) showed that an HV state may lead to the acquisition of fear responses to neutral stimuli. The heightened susceptibility to phobic fears mediated by relative hypocapnia, which returns each month, may thus account for the high incidence of female phobic responses. While this hypothesis based on existing data does, indeed, appear to be supported, further research in which the alkalosis is manipulated experimentally will be needed before such an explanation can be accepted as a general truth (chapter 3.5 experiments I & II).

2.1.3 Cognitive variables

This paragraph is based on: G.M. van der Molen en M.A. van den Hout (1987). Interoceptieve angst bij neurotische paniek: een drietal gecontroleerde studies. Gedragstherapie 20(3), 177-190.

As was already noted in the previous paragraph, it is possible to study psychopatho-

logical conditions in a laboratory setting, by inducing symptoms with a pharmacological intervention. This experimental approach has the advantage that different aspects of anxiety can be readily studied without the need to wait for spontaneous panic attacks to occur. An ideal model of anxiety should meet several criteria: the induced anxiety, and therefore both peripheral and central manifestations should be fostered; it should be replicable and reversible, and it should differentiate between "normal" and pathological subjects (Guttmacher et al., 1983).

Since Pitts and McClure's first experiments (1967), at least 18 replications have confirmed that an infusion of half-molar d,l-lactate induces autonomic symptoms reminiscent of panic. Lactate infusion triggers full-blown panic attacks in about 60 to 90% of panic patients, but only in about 10% of non-patients (see: Margraf et al., 1986). The validity of the lactate model appears obvious. However, the pathogenesis of panic is still obscure. It is clear that a variety of pharmacological agents can trigger panic attacks. The effects of bicarbonate (Grosz & Farmer, 1969; 1972), isoproteronol (Freedman et al., 1984; Rainey et al., 1984), carbondioxide (Griez et. al., 1987; Gorman et al., 1984; Fyer et al., 1987), caffeine (Charney et al., 1985), and most of all lactate (Guttmacher et al., 1983; Liebowitz et al., 1984; 1985; Margraf et al., 1986) are quite well documented. Summarizing, it can be stated that these agents trigger a great variety of physiological and biochemical changes and internal sensations both in patients and in normals, whether they panic or not. It is remarkable that the majority of the panic patients report panic on these challenges while normals do not.

A cognitive-physiological explanation of panic

The question of the diagnostic specificity of these challenges is of crucial importance: why do panic patients react with great terror whereas normals do not? A specific biological vulnerability has been suggested. The biological models of Klein (1981) and Sheehan (Carr and Sheehan, 1984) are the most elaborate ones to date and they have been very influential.

The interaction between bodily symptoms, external variables and cognitive factors probably offers an alternative explanation for both experimental and natural panic. Several models explain panic by conditioning to interoceptions that happen to be part of the anxiety response (Eysenck, 1968), a phobo-phobia (van den Hout and Griez, 1983), fear-of-fear (Evans, 1972), catastrophic misinterpretation (Clark, 1986), and the like. These alternative explanations all have in common that they observe that the perception and

interpretation of bodily symptoms can lead to panic (Ackerman and Sachar, 1974). The essential characteristic of a cognitive physiological explanation is that the perception of bodily sensations such as palpitations, dizziness, dyspnea etc. are interpreted as forecasting something terrible. It can be argued that fear of introceptive sensations is a maintaining factor in panic disorder. Contrary to anxiety in simple phobias, panic attacks in panic patients are, by definition, not elicited by specific environmental cues. These attacks may, however, be triggered by certain bodily sensations. Just as environmental cues may trigger phobic anxiety in subjects suffering from simple phobia, the perception of certain bodily feelings may induce fear in others and more specifically, it may be argued that panic patients suffer from a fear of those interoceptions that also happen to be part of the physiological anxiety response. Panic only develops, when these sensations are labeled as threatening or as signals for great danger. These anxious thoughts multiply the physical symptoms. So this explanation suggest that the development of fear can best be described as a self-maintaining, positive feedback loop. Minor internal stimuli, once felt, produce anxiety, amplifying the frightening sensations, and mediated by cognitive processes increasing anxiety and so on.

Many of the physiological and biochemical changes induced by lactate infusions (Liebowitz et al., 1985) can be perceived and, following the cognitive perspective, may be misinterpreted by the panic patients. Thus, an anxiogenic misinterpretation of lactate induced interoceptions would, at least partly, explain why most patients panic on lactate while normals do not. From this model some predictions can be made, which can be tested empirically.

First, this model predicts diagnostic specificity, that is that interoceptive fear may not be reported by normal controls and it may neither be characteristic of any other neurotic disorder. A questionnaire study suggests that interoceptive fear is indeed specific to PD and that this specificity is reflected in self-reported fear (Van den Hout, van der Molen, et al., 1987).

Second, it is predicted that habituation will occur when panic patients are repeatedly exposed to the sensations feared. This must lead to reduction of anxiety. In a single-blind placebo controlled patient-control study it was shown that strong reductions of anxiety occur when patients are repeatedly confronted with carbondioxide inhalations which elicit the feared sensations (Van den Hout, van der Molen, et al., 1987a).

Third, when patients panic because of their habitual mislabeling of bodily sensations, these cognitive factors could be responsible for experimental panic. Anecdotal indications

are found in literature: *I would have panicked, but for your presence doctor* ... (Bonn et al., 1971), but the tenability of a cognitive-physiological explanation of experimentally induced panic has hardly ever been investigated. It is of interest to note that in most of the lactate studies, patients were warned in advance that they could expect a panic attack. It is highly conceivable that in these studies the pre-infusion instructions increased the risk of an anxiogenic interpretation (Appleby et al., 1981)

Patients were told that they might experience a panic attack and knew basically what to expect. Controls too were told that they might experience an attack with symptoms analogous to those of public speaking ...

In recent literature three other indications are found that this approach to panic may be justified. In a carbondioxide study, normal healthy subjects who were told that inhalation would produce a state of pleasant relaxation reported a confirming change (Van den Hout & Griez, 1982). Rapee et al. (1986) subjected patients with panic attacks and patients with social phobia to 50%CO_2/50%O_2 inhalation. Half of each diagnostic category received either no explanation or a full explanation about all sensations and effects of the gas that would be possible. Social phobics of both groups reported effects similar to each other, regardless of the explanation given. Panic patients without any explanation, reported greater panic than those who received full explanation (Rapee et al., 1986). Finally, Margraff et al. (1988) were capable of manipulating anxiety responses to HV provocation, due to experimental instruction.

2.2
Research hypotheses

The theoretical considerations outlined above gave rise to several hypotheses. These are summarized below.

The question of specificity of influence of childhood experiences and personality traits, in the etiology of agoraphobia and panic disorder, is reflected in the following hypotheses:

1.

Patients suffering from agoraphobia or panic disorder, have been separated more from their parents in youth or childhood than both non-panicking, non-agoraphobic patients, and healthy control subjects without psychological complaints (chapter 3.1).

2.

Patients suffering from agoraphobia or panic disorder have suffered more from childhood separation anxiety than both non-panicking, non-agoraphobic neurotic patients, and healthy controls without psychological complaints (chapter 3.1).

3.

Patients suffering from agoraphobia or panic disorder, are more externally oriented, as measured with the Rotter IE-scale, than both non-panicking, non-agoraphobic neurotic controls, and normal controls (chapter 3.2).

From existing literature, the close relationship between alkalosis and panic became clear. Thus, susceptibility to the acquisition of phobic fears may be mediated by a relative hypocapnia. It was hypothesized that a lowered pCO_2 in itself may facilitate the acquisition and inhibit the extinction of conditioned fear:

4.

In subjects in a state of subjective anxiety, due to experimental manipulation, pCO_2 will be depressed as compared to subjects who went through the same experimental manipulation, but were non-anxious (chapter 3.4).

5.

Women in the premenstrual phase of their menstrual cycle will show a facilitated acquisition and a resistance to extinction of conditioned fear (chapter 3.3).

6.

Subjects in a state of respiratory alkalosis during acquisition of a conditioned electrodermal response, will show a facilitated acquisition and the extinction of these responses will be delayed (chapter 3.5 - experiment I).

7.

Subjects in a state of respiratory alkalosis during extinction of a conditioned electrodermal response - who were in a state of normocapnia during acquisition of this response - will show a delayed extinction of this response (chapter 3.5 - experiment II).

The cognitive-physiological interpretation of panic discussed in the previous paragraph predicts that patients panic because of their habitual mislabeling of bodily sensations. Therefore it must be possible to induce panic in normal subjects when the cognitive set is manipulated by experimental instruction in such a way that subjects will interpret the sensations induced by experimental manipulation as dangerous.

8.

Healthy volunteers without anxiety complaints, subjected to lactate infusion and "anxiety instruction" will show increased subjective anxiety during lactate, while subjects subjected to "pleasant excitement instruction" will not.

CHAPTER THREE

INTRA-SUBJECT DETERMINANTS OF ANXIETY

EXPERIMENTAL STUDIES

The following chapter consists of 6 separate articles. Except for 3.5 they have all been published or accepted for publication. The study described in chapter 3.5 sought to find answers to the questions that were formulated in the NWO-project 560-268-001. Some overlap in the introductory paragraphs is inevitable and some people may consider this a disadvantage. On the other hand this will offer the reader the possibility to follow the parts of interest in random order.

3.1

CHILDHOOD SEPARATION ANXIETY

No specific precursor to panic disorders

G.M. van der Molen, M.A. van den Hout, A.C. van Dieren & E. Griez. Journal of Anxiety Disorders (accepted for publication).

Abstract

The similarity between the symptoms of separation anxiety and those of agoraphobia may be of etiological significance. The hypothesis that early object loss and/or separation anxiety specifically predisposes one to agoraphobia or panic disorder is incorporated into DSM-III. The purpose of the present study was to test this hypothesis. Forty-one patients with agoraphobia or panic disorder were compared with 83 non-panicking neurotic controls and 50 normal controls. The three groups did not differ in actual parental separation (death of one or both parents, divorce, boarding school, etc.). 10% of the normal controls had suffered from separation anxiety according to DSM-III criteria, as did 17.5% of the agoraphobics and 35.4% of the neurotic controls. The only significant difference found was between neurotic and normal controls. The present data do not support the hypothesis that separation anxiety selectively leads to agoraphobia or panic disorder in later life. Childhood separation or separation anxiety probably reflects some general susceptibility to future neurotic behavior. The findings are discussed in the context of existing literature.

Introduction

There is little information regarding the etiology of agoraphobia and panic disorder. The obvious similarity between agoraphobia and panic disorder (APD) in adults and separation anxiety in children offers an interesting perspective. While children with separation anxiety typically react with extreme terror when separated from their parents, many, if not most agoraphobics may experience full-blown panic attacks when unaccompanied by their partner or family members in public places. This symptom similarity may be of etiological significance as it raises certain questions. Are children of APD parents more susceptible to separation anxiety than children of parents without agoraphobia or panic

disorder? Does separation anxiety in childhood predispose one to agoraphobia or panic disorder in adulthood?

With regard to the first question, several studies have investigated whether parental APD is associated with anxiety in children. When considering these studies, Weissman & Merikangas (1986) concluded that anxiety neurosis does, indeed, run in families. An extensive review of family and twin studies (Carey & Gottisman, 1981) supports the specificity of genetic transmission in panic disorder. Tøgerson (1983) found a significantly higher concordance rate for agoraphobia and panic disorder in monozygotic twins than in dizygotic twins. However, data do not permit conclusions to be drawn as to whether the transmission is genetic or cultural (Moran & Andrews, 1985).

Acknowledging the fact that school phobia and separation anxiety are quite similar in many aspects, a survey study on agoraphobic women (Berg, 1976) provides some evidence that parental agoraphobia does, indeed, predispose the child specifically to separation anxiety. School phobia occurred more often in children of agoraphobic women than in general population. Moreover, agoraphobic women with school phobic children had suffered more from school phobia themselves and had more severe complaints than agoraphobic women without school phobic children. Impressive evidence that parental APD does, indeed, increase the risk of children's separation anxiety was provided by Weissman et al. (1984). They investigated the psychiatric state of the children of parents with major depression associated with agoraphobia, panic disorder or Generalized Anxiety Disorder (GAD). Both agoraphobia and Panic Disorder (PD) conferred an additional risk of depression and/or anxiety neurosis in children. PD in the parent led to more than a threefold risk of separation anxiety in the children.

The second etiological question concerns the transposition of childhood separation anxiety to adult APD. Though parental APD may increase the risk of separation anxiety in offspring and though it is acknowledged that anxiety neurosis runs in families, it is not necessarily true that childhood separation anxiety predisposes a particular individual to APD. Several authors, indeed, maintain that early parental separation and, more specifically, childhood separation anxiety are associated with the development of agoraphobia or panic disorder. This conviction is incorporated into DSM-III, stating that separation anxiety in childhood predisposes one to the development of both agoraphobia and panic disorder. Empirical data to support the assumption that childhood separation anxiety is a developmental antecedent of APD are far from equivocal.

When studying this crucial etiological issue, a distinction must be made between sep-

aration anxiety and actual separation. There is little question that early separation may be considered a highly traumatic event. The importance of the availability of attachment figures is often stressed (Bolwby, 1973). In animal studies, it is well documented that early separation can lead to immediate panic-like behaviors and "depressions" in the long run (Coe & Levine, 1983; Timmermans et al., 1986). In controlled human studies, early separation has been reported more often by agoraphobic patients than by normal controls (Faravelli et al., 1985), more often by APD than by GAD patients (Raskin et al., 1982), and more often by agoraphobics than by social phobics (Person & Nordlund, 1985). On the other hand, early separation also seems to be a risk factor for non-endogenous depression (Roy, 1985) and for phobic behavior in general (Aitkens et al., 1981). Though more research is needed, it can tentatively be concluded from the available findings that APD may, indeed, be characterized by a relatively high incidence of actual separation at an early age.

Data on separation anxiety as a precursor to APD mainly stem from clinical observations (Klein, 1964; Gittelman-Klein, 1975; Gittelman-Klein & Klein, 1973). In an extensive study on agoraphobia, Breier et al. (1986) report that 18% of the APD patients studied had suffered from separation anxiety in childhood; no percentages are mentioned for control groups. Berg et al. (1974, 1974a) report 22% of their agoraphobics admitting to previous school phobia. However, this percentage is quite similar to that found in non-agoraphobic neurotic controls. These findings are very much in line with those of Raskin et al. (1982), who found no differences in early separation anxiety between PD and GAD patients. School phobia had occurred more frequently in psychiatric patients than among controls (Tyrer & Tyrer, 1974). When patients in this study, suffering from phobia, depression, and chronic anxiety were compared, the phobic patients tended to show a higher incidence of school phobia than the two other patient groups, yet no statistical significant differences were detected.

Recently, two controlled studies were conducted by Thyer et al. (1985, 1986) to test the separation anxiety hypothesis. In the first study, the authors compared 44 agoraphobics with 83 simple phobics. On 14 questions involving reported childhood separation experiences, the two groups did not differ significantly. In the second study, 23 panic disorder patients were compared with 28 small animal phobics. Again, no clear differences emerged between the groups. These data run contrary to the widely held belief in the separation anxiety hypothesis.

Acknowledging the importance of this issue as well as the need for a reliable body of

knowledge, we tested the hypothesis that both actual childhood separation and childhood separation anxiety are developmental antecedents of agoraphobia and panic disorder.

Conclusions regarding the diagnostic specificity of such antecedents should, of course, not only be based on comparisons between APD and normal controls, but should also include data from a neurotic control group without complaints of an agoraphobic nature. In the present study, patients treated for panic disorder or agoraphobia with panic attacks (APD) were compared with both a non-panicking neurotic control group (NPNC) and a normal control group (NC). Questions relating to separation anxiety were directly derived from the diagnostic DSM-III criteria for childhood separation anxiety.

Method

Subjects

Forty-one patients with panic disorder or agoraphobia (21 male, 20 female; aged 18-52 years, mean = 36.3) were compared with 83 non-panicking neurotic controls (27 male, 55 female; aged 18-65 years, mean = 36.6) and 50 normal controls (20 male, 30 female; aged 21-61 years, mean = 38.1). The patients were all treated at the Academic Department of Clinical Behavior Therapy at Vijverdal Psychiatric Hospital, Maastricht, The Netherlands.

Patients were first diagnosed according to DSM-III criteria after an intake interview by a member of the clinical staff. The diagnosis were cross checked by an other member of the research project. The NPNC included patients suffering from the following disorders: eating disorder (n = 25), obsessions and compulsions (n = 17), simple phobia (n = 7) social phobia (n = 7), depression (n = 7), personality disorder (n = 5), and other (n = 15). Normal controls, without any prior or current psychiatric complaints, were recruited from the general population (e.g. members of local sports clubs, family of the nursing staff, etc.).

Procedure

Each subject completed a brief questionnaire consisting of three parts. Part A included questions about actual separation in childhood. Questions regarding the death of parents and divorce were to be answered "yes" or "no"; in the event of the former, the age was noted. Questions regarding other separations (foster home, boarding school, etc.) were also to be answered "yes" or "no". In the former case, subjects indicated how pleasant or unpleasant they experienced these separations as being (1 = very unpleasant,

5 = very pleasant).

Part B included questions about neurotic problems in childhood; answers were given as either "present" or "absent".

Part C included questions about separation anxiety. These questions were based on the nine criteria from DSM-III childhood separation anxiety (see table 1). Criteria 1,4,6,7 and 9 were divided into two-part questions, bringing the total number of questions to 14. In the instructions to the questionnaire, subjects were asked to indicate to what extent they considered the statements relevant to their particular childhood and youth situations.

DSM-III criterion	question	Mean scores NC	APD	NPNC
(1)	1. I worried about possible harm happening to my parents.	1.52	1.92	1.95
	2. I worried my parents would leave and not return.	1.12	1.35	1.68
(2)	3. I worried that a serious event (an accident, a disaster, or kidnapping) would separate me from my parents.	1.34	1.42	1.74
(3)	4. I was reluctant to go to school in order to stay with my parents.	1.28	1.37	1.56
(4)	5. I was reluctant to go to sleep when my father or mother was not close to me.	1.40	1.70	1.70
	6. I refused to sleep away from home.	1.38	1.80	1.75
(5)	7. I avoided being alone at home.	1.64	1.65	2.00
	8. I got upset when I was unable to follow my father or mother around the house.	1.08	1.22	1.39
(6)	9. I had repeated nightmares that I would be separated from my parents.	1.06	1.27	1.42
(7)	10. On school days, I suffered from stomachaches, headaches, nausea, vomiting and the like.	1.24	1.65	1.95
(8)	11. I had temper tantrums or cried when I could not stay with my parents.	1.12	1.30	1.46
	12. I pleaded with my parents not to go away when I expected them to leave.	1.10	1.37	1.45
(9)	13. I withdrew from contact with others when my parents were not around.	1.22	1.52	1.67
	14. I was sad and apathetic and could not concentrate on work or play when my parents where not around.	1.14	1.27	1.66

Table 1: Questions about Separation Anxiety Disorder and the mean scores on these items for the three different groups.

Answers were given on a 5-point scale, with 1 indicating "not at all" and 5 indicating "extremely".

Results

Part A: Actual separation

Data on separation from parents during childhood are represented in table 2. Differences were tested with χ^2. The three groups did not differ in death of one or both parents. Nor did the three groups differ with regard to the number of divorced parents. Though the percentage in the NPNC tended to be somewhat higher than in both the NC and APD groups, the three groups did not differ in separation from parents for reasons other than death and/or divorce. NPNC rated these periods of separation as more unpleasant than either NC or APD (table 2).

Part B: Neurotic problems in childhood

Data on childhood problems are presented in table 3. The number of subjects having suffered from these problems tended to be lower in NC than in APD or NPNC. One-way analysis of variance over the mean total number of problems (NC = 0.94; APD = 2.17; NPNC = 2.20) revealed significant differences between groups ($F(2,173) = 9.48$; p.01). Subsequent Sheffé testing showed that NC reported significantly fewer problems than APD or NPNC ($p < 0.01$). No differences were detected between APD and NPNC. None of NC saw professional help for childhood problems, while 2.9% of APD and 10.2% of NPNC did.

Part C: Separation anxiety

The mean scores for each item involving separation anxiety are represented in table 1. As can be seen from the table, there was a tendency for the NPNC to score higher than the APD and NC. Reliability analysis revealed a highly consistent questionnaire ($\alpha = 0.93$), so individual raw scores could be added and mean scores computed. The mean scores, with the standard deviation given between brackets, were 17.3(4.6), 20.7(11.4), and 23.3(11.2) for NC, APD, and NPNC respectively (Figure I). One-way analysis of variance showed differences between groups ($F(2,164) = 5.58$; $p < 0.01$). Sheffé testing showed that NC differed from NPNC. No differences were found between APD and NPNC.

	Percentage of cases			Score on "pleasantness"		
	NC	APD	NPNC	NC	APD	NPNC
divorce	4.0	7.5	6.0			
mother died	6.1	2.5	3.6			
father died	6.1	5.0	4.8			
both parents died	2.0	2.5	1.2			
staying over at relative's house	11.6	57.5	64.2	3.9	3.5	3.2*
summer camp	33.8	40.0	37.0	3.8	3.8	2.8**
hospital	24.5	27.5	40.5	2.5	2.0	2.1
boarding school	4.1	2.5	9.9	1.5	-	1.4
foster home	0.0	2.5	8.6	1.0	1.1	1.2
other	8.2	5.0	9.9	4.7	2.5	1.7*

* NPNC < NC; $p<0.05$

** NPNC < NC, APD; $p<0.05$

Table 2: Percentage of subjects indicating separation from their parents during childhood (left panel) and scores of experienced "pleasantness" during these periods of separation (right panel).

	NC	APD	NPNC	χ^2, (with Yates correction)*
nightmares	10.0	17.1	19.3	
enuresis	2.0	9.8	13.3	p<0.10
anxieties	12.0	53.7	59.0	p<0.001
head-bouncing	10.0	4.9	19.3	p<0.10
stuttering	8.0	2.4	8.4	
sleepwalking	8.0	7.3	10.8	
hyperactivity	6.0	56.1	38.6	p<0.001
temper tantrums	12.0	26.8	21.7	
distructive behavior	0.0	12.2	8.4	p<0.10
nail biting	26.0	24.4	22.9	
professional help	0.0	4.9	9.6	p<0.10

* All differences are caused by the fewer cases of NC, than both APD and NPNC. No statistical significant differences between APD and NPNC emerged.

Table 3: Percentage of subjects indicating childhood problems and seeking professional help.

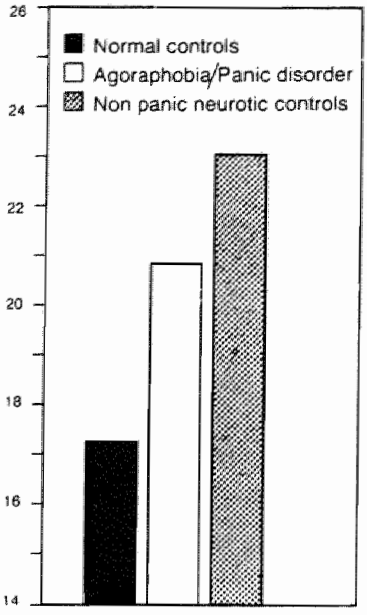

Figure I: Mean scores on 14 separation anxiety items for three different groups.

Diagnosis of separation anxiety is not made on the basis of a continuous scale, but rather when "3 out of 9 symptoms" are present (DSM-III). Thus, some additional analyses were made on the basis of the criterion: "3 out of 9 symptoms", scoring 3. According to this analysis, 10.0% of NC, 17.5% of APD, and 35.4% of NPNC suffered from separation anxiety. (These percentages are 16.0, 37.5, 57.3, and 6.0, 12.5, 17.5 for scoring 2 and 4, respectively).

Discussion

The hypothesis that early actual separation from parents predisposes one specifically to APD was not confirmed. Both APD and NPNC tended to have experienced a more disturbed parental environment than NC. Neurotic controls rated these periods of separation as more unpleasant than either NC or APD.

The second hypothesis, that separation anxiety specifically predisposes one to APD, was not confirmed either. While it was found that non-panicking neurotic controls scored higher than the normal control group, APD could not be identified as different from either

NPNC or NC.

Actual separation during childhood

Based on differences between PD and GAD, Raskin et al. (1982) concluded that childhood separation anxiety predisposes one to APD. The present data, however, refute this conclusion. Person and Nordlund (1985) also reported early separation and a disturbed parental environment occurring more often in agoraphobics than in social phobics. In their discussion of the data, however, they note that these differences disappear when a correction is made for SES. Faravelli et al. (1985) reported an association between early separation and APD. However, this association only exists when all kinds of separations are included. In their study, separation by death of the father or mother did not differ between groups while separation as a result of divorce did. No reference was made to a normal control group. In our sample, divorced parents and death of parents tended to occur more often in APD than in NC, but no statistically significant differences were found. On the other hand, these separations tended to occur even more often in NPNC. The patients in the Faravelli study (1985) also differed in traumatic childhood experiences. This is not unlike our finding that both NPNC and PD had more neurotic problems in childhood than NC and saw professional help more often.

The separation anxiety hypothesis

The finding that APD did not differ from NPNC was a refutation of the hypothesis that separation anxiety in childhood is a diagnostically specific criterion for agoraphobia or panic disorder. These results are consistent with the findings of Thyrer et al. (1985, 1986). They did not find any differences in history of childhood separation anxiety between simple phobics, and agoraphobics or panic disorder patients; however, no comparison was made with a normal control group. Their study differed from ours in that their questions about separation anxiety were asked in more general terms. Moreover, no difference was made between separation and separation anxiety.

When the DSM-III criterion "3 out of 9 symptoms present" and a score 3 per item was applied, 17.5% of APD suffered from separation anxiety. This percentage is about the same as that found by Breier et al. (1986) for an American agoraphobic/panic population (18%). This number is higher than the 10.0% in the NC but smaller than the 35.4 in the NPNC. Thus, our data seem to lead to the conclusion that childhood separation anxiety reflects some general susceptibility to future neurotic behavior, rather than a predisposi-

tion to APD in particular.

An important methodological issue in this kind of research involves the possible distorting effects of time on memory. This study was ex post facto and obviously only prospective trials can yield definite answers. Yet, people tend to overrate the stability and consistency of their actual behaviors over time, while memories with an affective coloring comparable to the present affective state are more easily accessible. Thus, the retrospective nature of the present study might have been a bias in favor of the hypothesis. The fact that NPNC subjects, who have no actual complaints of a separation anxiety nature, in fact score higher than APD subjects, may constitute an a fortiori argument against the hypothesis tested. Whether the tendency of NPNC and APD to score high (higher than NC) is historically justified is impossible to tell. One should not rule out the possibility that elevated scores may, at least in part, be explained by actual neuroticism.

Data from the present study tentatively show that empirical inclusion, not only of normal controls but also of other neurotic controls, is of vital importance when trying to detect specific features of agoraphobic or panic patients. In DSM-III criteria for agoraphobia and panic disorder, it was stated that "Separation anxiety disorder in childhood (...) apparently predispose to the development of this disorder". Despite the little controlled research to support the separation anxiety hypothesis, it is still present in DSM-III-R.

We would suggest that the DSM-III-R assumption of separation anxiety as a selective precursor for panic disorder be reconsidered.

3.2

AGORAPHOBIA AND LOCUS OF CONTROL

G.M. van der Molen, M.A. van den Hout & R. Halfens. Journal of Psychopathology and Behavioral Assessment, 10(3), 1988.

Abstract

This study investigated whether external locus of control, as measured with the Rotter Internal-External Locus of Control Scale, is a specific feature of agoraphobia or whether it characterizes neurosis in general. Forty agoraphobic patients, 81 non-agoraphobic neurotic controls, and 49 normal controls completed the Dutch version of the Rotter Internal-External Locus of Control Scale. Agoraphobic patients were found to have a more external orientation as compared to the normal controls but, as a group, they could not be identified as being different from neurotic controls.

Introduction

Specific personality traits have been assumed to predispose one to agoraphobia. Agoraphobic patients have been characterized as dependent, timid, shy, anxious, depressive, unassertive, immature and the like (Marks, 1969; Chambless, 1982), but there is little empirical evidence that a clear "agoraphobic personality" exists. Agoraphobia is a phobia that stands somewhat on its own in the class of phobias. Agoraphobic patients experience a terrifying, irrational fear of public places. However, it is not these stimuli or places as such that elicit the agoraphobic fear. Rather, it is the feeling of helplessness or the loss of control that the patient might experience during a panic attack in these places that the agoraphobic fears. From a clinical perspective panic disorder and agoraphobia are closely related disorders. Some agoraphobic patients describe panic attacks that occur in non-phobic situations (Barlow et al., 1985) and many report the development of agoraphobic fears following the onset of periods of seemingly spontaneous panic attacks (Sheehan et al., 1980). On the other hand, in patients treated for panic disorder, many show varying degrees of agoraphobic avoidance. Recent investigations have supported the view that agoraphobia could be a complication of panic disorder (Thyer & Himle, 1985). In an extensive study of patients who met DSM-III criteria for panic disorder and agoraphobia Thyer

et al. (1985) could not demonstrate any meaningful differences in demographic, psychometric or clinical features between the two groups. These data seem to support the view that panic disorder and agoraphobia are indistinguishable in terms of relevant nosological features.

Fear of having an attack appears to be an essential feature of agoraphobia. It seems that agoraphobic and panic patients are unaware of the origin of their anxiety and feel unable to avoid or to cope with these anxiety episodes. They typically appear to attribute their anxiety to processes beyond their control, e.g. cardiovascular malfunctioning. Persons perceiving reinforcements not being under their personal control, but as the result of chance or fate, are indicated as having an "externals locus of control" (Rotter, 1954). Therefore, it has been suggested that an important psychological factor to consider in the genesis of agoraphobia is locus of control (Emmelkamp, 1982; De Moor, 1985).

Since Rotter, Seeman and Leverant (1962) introduced it, the scale for measuring the locus of control (IE-scale) has been used in many studies and in a wide variety of situations. The scale was developed as part of Rotter's social learning theory. A subject learns to see the relationship between his behavior and the outcomes either as something he himself controls or as something determined by external factors. (Rotter, 1954; Rotter, Chance & Phares 1972). The IE-scale measures generalized expectancies for internal and external control of reinforcement. Subjects whose scores on the IE-scale indicate internal locus of control are referred to as "internals", those whose scores indicate external control as "externals". Externals are more likely to develop such behaviors as passivity, conformity, compliance, and withdrawal, than internals. This cluster of behaviors is usually manifested by persons experiencing uncontrollability.

In some studies it has been demonstrated that external locus of control is related to agoraphobia (Emmelkamp and Cohen-Kettenis, 1975; Adler & Price, 1985). Hoehn-Saric & McLeod (1986) showed that patients with an external locus of control exhibited more agoraphobia than those with an internal locus of control. Though these studies suggest a relationship between external orientation and agoraphobia, the question remains whether external locus of control is a specific feature of agoraphobia and panic disorder. The concept of locus of control may be non-specific, since it is not clear whether external locus of control is also associated with other diagnostic groups. An indication of non-specificity is given by Johnson & Sarason (1978). Noting that internals and externals respond differently to life-events, they found in a study on life-stress, that locus of control turned out to be an important moderator variable both in the development of anxiety and of depression.

Harrow & Ferrante (1969) showed in a sample of acute psychiatric inpatients that patients with greater psychopathology are more external.

The question of internal or external locus of control is also important from a therapeutic point of view. In general, studies investigating the relationship between locus of control, and therapy expectation and outcome, suggest that internals are expected to be more successful. Internals are also tending toward more successful treatment outcomes (Foon, 1987). In studies matching locus of control with treatment it was found that patients with an internal locus of control benefit most from non-directive, unstructured, analytic approaches. External patients, however, prefer directive, structured techniques and passive acceptance of medication (Kilmann et al., 1975; Hoehn-Saric & McLeod, 1985; Foon, 1987). In a study on the prognostic utility of locus of control in the treatment of agoraphobia, externality was strongly associated with improvement in a behavioral and pharmacological treatment program (Michelson et al., 1983).

The aim of the present study was to directly test the specificity of external locus of control to agoraphobia and panic disorder. A comparison was made between the locus of control orientation in three groups: agoraphobic/panic patients, normal controls, and patients with neurotic complaints of a non-panic, non-agoraphobic nature. It was hypothesized that panic and agoraphobic patients are more externally oriented than both normal controls and neurotic controls.

Method

Forty patients with agoraphobia or panic disorder (APD) (21 male, 19 female; age 18 - 52 years, M = 38.1) were compared with 81 non-agoraphobic, non-panicking neurotic controls (NANC) (27 male, 54 female; age 18 - 65 years, M = 36.6) and 50 normal controls (NC) (19 male, 30 female; age 21 - 61 years, M = 36.6). The patients were all treated at the Academic Department of Clinical Behavior Therapy at Vijverdal Psychiatric Hospital, Maastricht, The Netherlands. Patients were first diagnosed after an intake interview by a member of the clinical staff according to DSM-III criteria: agoraphobia with or without panic, or panic disorder. The diagnosis were cross checked by an other member of the research project. The NANC was comprised of the following subsamples: obsessions and compulsions (n = 17), eating disorder (n = 25), simple phobia (n = 7), depression (n = 6), social phobia (n = 7), personality disorder (n = 4), other (n = 15). Normal controls, without any prior or current psychiatric complaints, were recruited from the general popula-

tion (members of local sporting clubs, family of nursing staff, etc.).

Subjects completed the Dutch version of the Rotter IE-scale (Andriessen, 1972; Andriessen & Van Cadzand, 1983). The questionnaire consisted of 18 questions. Raw scores ranged from 18 to 108, the higher the score, the more external the orientation was.

Results

Principal component analysis revealed a single factor structure (30.3% variation explained by the first factor), suggesting that this scale measured a unitary construct. Reliability analysis revealed a highly consistent scale (α = 0.86). After adding individual raw scores, mean scores for the three groups could be computed. Means and s.d. (between brackets) for NC, APD and NPNC were 55.4(10.8); 60.8(13.4) and 64.6(14.2), respectively. The data are presented in Figure 1.

One-way analysis of variance showed significant differences between groups ($F(2,163) = 7.45$, $p < 0.01$). Scheffé testing showed that NC differed from NANC and APD ($p < 0.05$, $0.10 < p < 0.05$ respectively). No significant differences were found between APD and NANC.

No significant differences for sex or age were detected.

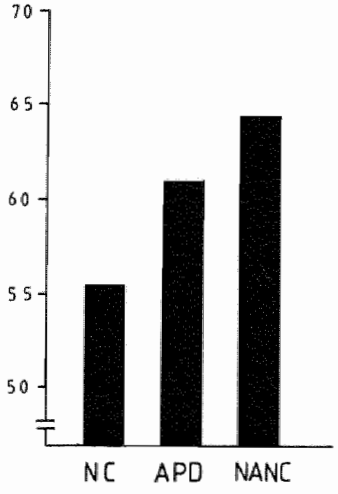

Figure 1. Mean scores on the IE-scale for agoraphobic/panic patients (APD), normal controls (NC) and non-agoraphobic, neurotic controls.

Discussion

The hypothesis that external orientation is specific to agoraphobia/panic disorder was not confirmed. While it was found that APD did not score higher on the IE-scale than did the NPNC group, both neurotic samples displayed a more external orientation than did the normal control group.

In one respect, the high external orientation as compared to control of both the neurotic groups may not be surprising: typically neurotics suffer from invalidating fears, habits etc., which are recognized as irrational but nonetheless are experienced as being beyond voluntary control. This general feature is not dissimilar to the notion of externality as measured by Rotter's IE-scale. Whether an external orientation promotes the development of neurotic symptoms or vise versa is not quite clear. In a study on behavioral and pharmacological treatment of agoraphobia Michelson et al. (1983) found that locus of control score did not show any significant changes, even though patients showed marked clinical improvement. On the other hand Emmelkamp et al. (1978) showed that a significant change can occur after treatment. This was, however, found only in the special case that exposure in vivo was followed by cognitive modification. Ultimate proofs of cause and consequence in the relationship between external locus of control and neurotic symptoms should come from longitudinal studies.

The finding that APD did not differ from NANC was a disconfirmation of the hypothesis tested. Research on the relationship between locus of control and agoraphobia using only normal control groups should therefore be interpreted with care. A characteristic difference between APD and other neurotic patients is the occurrence of anxiety episodes that are experienced as coming "out of the blue". Apparently the experience of "spontaneous", unpredicted fears does not result from a diagnostically distinct high external locus of control. It would seem plausible that experiencing unpredicted fears would reduce feelings of self-efficacy or selfcontrol and would be reflected in an external orientation. However, from this study it seems clear that such is not the case. As to the attributional style of APD patients, investigations of symptom relevant cognitive peculiarities may be more fruitful than trying to distinguish the group on more global generalized mental habits.

The present study indicate that including not only normal controls but also other neurotic controls is of vital importance when trying to describe specific features of APD patients. Dissection of cognitive styles and contents that characterizes neurotic subgroups will provide an interesting field for further study.

3.3
MENSTRUAL CYCLE AND THE CONDITIONED
Skin conductance response

G.M. van der Molen, H. Merckelbach & M.A. van den Hout. The possible relation of the menstrual cycle to susceptibility to fear acquisition. Journal of Behaviour Therapy and Experimental Psychiatry, 19(2), 1988.

Abstract

Biological changes due to the menstrual cycle may account for the fact that fears are not equally distributed between the sexes. In a differential, classical conditioning paradigm, women, in pre-menstrual phase of their menstrual cycles were compared with a control group of women at other points in their cycles except within seven days before menstruation. Electric shock and pictures of natural scenes were used as UCS and CS respectively. Pre-menstrual women showed an enhanced susceptibility to the acquisition of a conditioned skin conductance response and to delayed extinction, while control women did not. The possible role of altered physiological state during the pre-menstrual phase in the acquisition of fear responses is discussed.

Introduction

The sex distribution of anxiety disorders, particularly that of agoraphobia, is skewed. About 2/3 to 3/4 of the afflicted individuals are female (Emmelkamp, 1982; Schutz, 1981). Biological processes are often said to play a role here. More specifically, it has been argued that the hormonal changes inherent in the menstrual cycle, and in the pre-menstrual phase in particular, predispose women to negative affect. While sociocultural factors may account, at least in part, for what has come to be called the "Pre-Menstrual Syndrome" (PMS) (Ruble and Brooks-Gunn, 1979), a biological basis for PMS is also finding some support these days.

First, clinical observation suggests that in anxious female patients, symptoms increase pre-menstrually. For instance, in a recent study conducted on the etiology of anxiety disorders (Breier et al., 1986), it was found that 22 out of 43 normally menstruating patients suffering from agoraphobia or panic disorder experienced a worsening of anxiety com-

plaints during a period of seven days prior to menstruation. Fourteen reported a remarkable increase in the number of panic attacks during this period.

Second, a good deal of research has been devoted to the relationship between hormonal changes during the menstrual cycle and vulnerability to a broad spectrum of emotional complaints and somatic symptoms. Most data, collected in retrospective self-report studies, demonstrate a wide range of negative mood changes that show a pre-menstrual peak (May, 1975; Wilcoxon et al., 1976). It should be noted that when prospective blind methods were used, no such dramatic effects could be demonstrated (Slade, 1984; Rubinov & Roy-Byrne, 1984;

Halbreich & Endicott, 1985). However, there are a series of pre-menstrual somatic changes that are not under volitional control, such as water retention and pain threshold (Wilcoxon et al., 1976), changes in acid-base balance (Damas-Mora et al., 1980), heart rate changes (Kuczmierzyck & Adams, 1986), low cortical alertness and high autonomic (electrodermal) reactivity (Asso, 1986).

Finally, experimental indication that the pre-menstrual state is etiologically related to neurotic fears comes from studies by Beech and colleagues. In their first study (Asso & Beech, 1975), 20 healthy women and 8 phobic women were subjected to a one-trial conditioning experiment, half of them pre-menstrually, the other half inter-menstrually. The conditioning trial consisted of one pairing of the conditioned stimulus (CS), a blue light, with the unconditioned stimulus (UCS), a loud noise. The skin conductance response (SCR) to three CS presentations, before and after the UCS-CS pairing, were compared in order to provide a measurement of the conditioned response (CR). Both the phobic and the normal women showed an enhanced reaction pre-menstrually, this effect being even more pronounced for the phobic group. These findings were confirmed in a second study (Vila & Beech, 1977) on 16 phobic patients. A somewhat more complex design was used this time, consisting of a one-trial "acquisition phase" followed by two test trials, and then two UCS-CS pairings followed by 10 extinction trials. The pre-menstrual women showed an increased susceptibility to the acquisition of SCR and possibly to resistance to extinction.

To the best of our knowledge, only one attempt to replicate these experiments have been reported. The results of that study (Strauss et al., 1983) were however not in line with previous findings. Considering that these studies, together with the Vila and Beech study (1978), in which a defensive heart-rate pattern was found in pre-menstrual phobic women, can be very important in the understanding of the development of neurotic fears, the auth-

ors decided to conduct a replication experiment.

A number of methodological considerations were taken into account. To begin with, since there is ample evidence of increased sympathetic activity in anxiety states (Lader & Mathews, 1968; Dietz, 1982; Sartory, 1983), skin conductance seemed an appropriate choice as independent variable for the study of anxiety. Next, if the etiology of anxiety is associated with the menstrual cycle, it can be argued that in pre-menstrual women either the acquisition of classically conditioned SCR will be facilitated or there will be resistance to extinction of stimulus-bound SCR, or possibly both. Therefore, it was decided that a delayed conditioning paradigm be used to allow for the measurement of CR on every CS and that acquisition and extinction phases be distinguished so that separate analyses of these phases would be possible. Since one-trial learning, as used in the Beech studies, may call for a rather intense UCS, another advantage of using a series of UCS-CS pairings is the use of a presumably less aversive UCS. To control for confounding factors, such as irrelevant features of the CS, a differential conditioning paradigm was used, in conformity with the studies by Öhman and co-workers (see: Öhman et al., 1978; Öhman,1986). Olasov and Jackson (1987) pointed to the role of expectations on the relationship between negative mood changes and menstruation. To limit this influence subjects were questioned about their menstrual cycles after the experiment. They received no information as to the CS-UCS contingency; subjects were only told that physiological reactions would be measured when looking at pictures of natural scenes. It was hypothesized that women in their pre-menstrual phase of menstrual cycle would show an enhanced susceptibility to the acquisition of a conditioned skin conductance response and to delayed extinction, when compared with women at other points in their cycles.

Method

Subjects

The subjects were 31 female undergraduate students with no history of psychiatric complaints. Their mean age was 21.2 years, with a range from 18 to 28 years. The subjects were blind as to the purpose of the study and were paid for their participation. During the experiment, they were seated in a comfortable chair in a dimly lit, sound attennuated chamber. The recording apparatus was in an adjacent room.

Apparatus and measurements

SCR and skin conductance level (SCL) were recorded by means of the constant voltage method (0,5 volts) (Venables & Christie, 1973). Beckman Ag/AgCL electrodes (ø = 8 mm) were attached to the middle phalanx of the second and third fingers of the left hand. The recording apparatus allowed for maximum sensitivity of 0.05 μμηο.

An electric stimulator with a maximum capacity of 40 mA delivered an electric current (DC, 0.5 sec.) to each subject. Two shock electrodes were placed on the first finger of the subject's left hand.

Slides were projected onto a white wall, 2.5 m in front of the subject. The size of each projected image, a picture of some natural scene, was approximately 80 x 120 cm. Projection lasted 8 sec. UCS immediately followed projection offset.

Experimental procedure, inter-trial intervals, occurrence of the electric pulses, slide onset and offset, etc. were accomplished by means of a PDP-11 computer. Since rate of conditioning is supposed to be linked to neuroticism, subjects filled out the "Amsterdamse Biografische Vragenlijst" (Amsterdam Biographical Questionnaire) (Wilde, 1962), the Dutch equivalent of the Eysenck Personality Inventory (Eysenck & Eysenck, 1964), which measures neuroticism.

Procedure and design

The experimenter explained that electric shocks would occur at some time during the experiment. After the subjects had given their consent, the experimenter started shock work-up procedure in which the shock level was gradually increased until the subject indicated that shock was "uncomfortable, but not painful". Subjects were not told about the CS-UCS contingency. Each subject saw two slides, one of which (CS^+) was followed by an electric shock (UCS) and the other (CS^-) not. CS^+ and CS^- slides were randomly varied over subjects.

The experiment consisted of three phases. The first was a habituation procedure. It involved the presentation of 8 unreinforced trials (4 CS^--alone and 4 to-be CS^+-alone). An acquisition phase then followed in which 6 CS^+-UCS pairings and 6 unreinforced CS^- presentations occurred. To study the course of differential response during acquisition, a CS^+-alone test-trial, that occurred halfway the acquisition phase, was added. Finally, there was an extinction phase consisting of 10 unreinforced presentations of both slides. The order of presentation of the two slides was quasi-random; no more than two successive presentations of the same slide occurred.

Analysis

After the experimental procedure, subjects were questioned about their menstrual cycles. A period of five days prior to expected menstruation is usually considered pre-menstrual (PM), but for cautions reasons we extended it to seven. By this conservative estimate eight women fell into this group. The others (n = 23), at other points in their cycles except within seven days before menstruation, made up the control group (C).

Response to CS was defined as a maximal deflection occurring 0-4 sec. after CS-onset. Thus CR's can be registered independently from the occurrence of the UCS. SCR and SCL were measured in μμηο ανδ σθυαρε – ροοτ τρανσφορμεδ ιν ορδερ το νορμαλιζε τηε διστριβυτιον (σεναβλεσ & Χηριστιε, 1973). Δατα ωερε αναλψζεδ ασ ρεσπονσε μαγνι – τυδεσ.

Using the t-statistic, group differences in mean shock level, resting SCL and neuroticism were examined. Separate three factor analyses of variance with repeated measures were carried out for the three phases of the experiment. The first was a Group factor (PM vs. C), the second a factor Stimulus (CS^+ vs. CS^-), and the third a repeated measure factor Trials. The rejection level for all comparisons was set at $p < 0.05$ (Greenhouse-Geisser prob.)

Results

The mean UCS level was the same for both groups 9.3 mA (sd = 6.4) in PM-women and 8.9 mA (sd = 5.5) in the C-women. These were moderate intensities, according to the criteria mentioned by Tursky (1973). There were also no significant differences in mean resting SCL ($M_{PM} = 4.26$, sd = 4.46; $M_C = 2.99$, sd = 4.59) or in neuroticism scores ($M_{PM} = 55.1$, sd = 15.1; $M_C = 57.5$, sd = 25.5).

SCR data are presented in Figure I. During habituation, the ANOVA revealed a significant Trials effect ($F(3,87) = 4.92$), indicating that habituation had occurred. No group differences were found.

Differences between groups emerged during acquisition and extinction. The significant Stimulus x Trials interaction ($F(5,145) = 2.92$) and the Trials factor ($F(5,145) = 2.20$) made it clear that the conditioning procedure had been effective; while responses to CS^- trials showed a progressive decrease, the responses to CS^+ increased. Post-hoc t-testing showed that this effect was due exclusively to differential responding in the PM-group

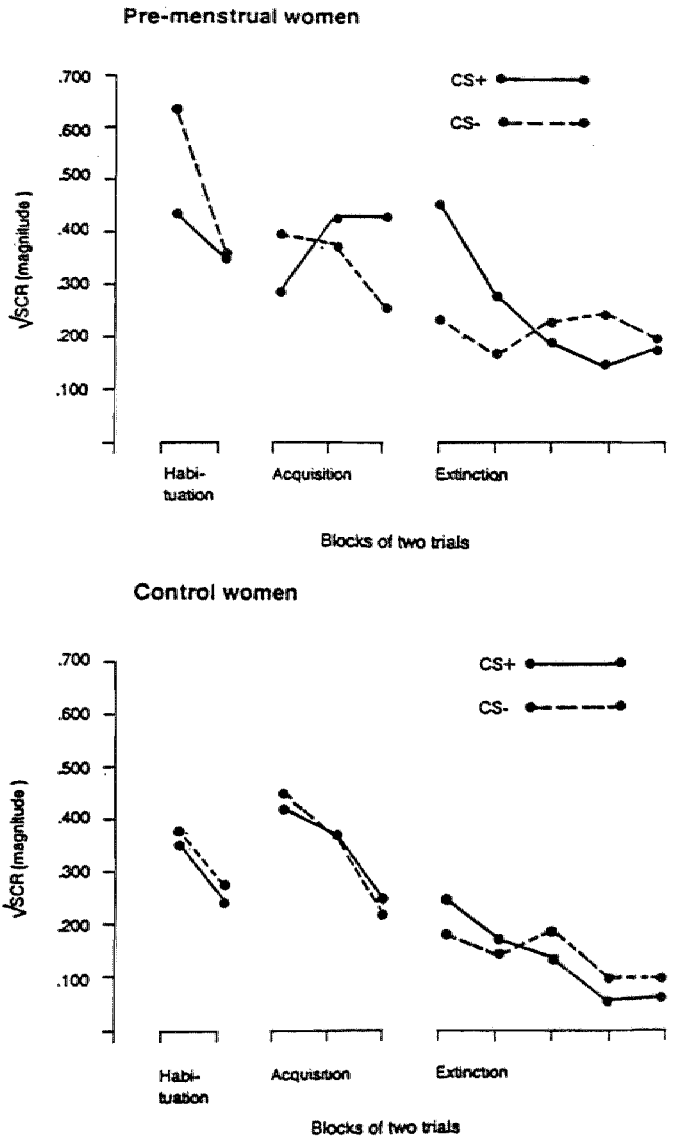

Figure I: Mean SCR to reinforced (CS^+) and unreinforced (CS^-) stimuli as a function blocks of 2 trials in pre-menstrual and control women.

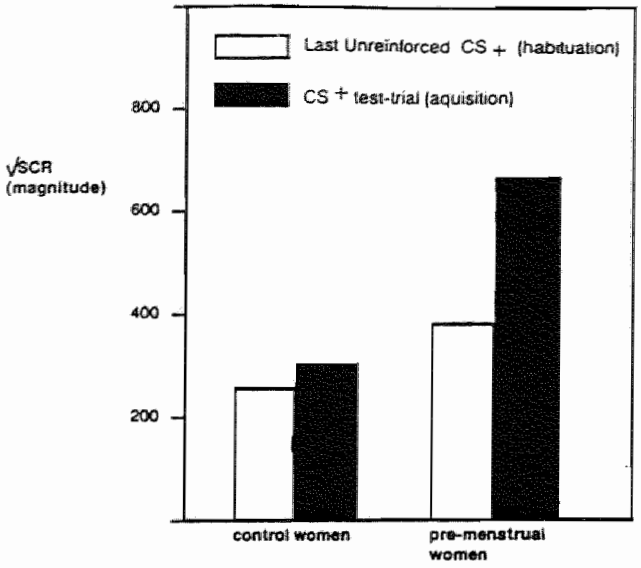

Figure II: Mean SCR to the last unreinforced CS$^+$ trial during habituation and an unreinforced CS$^+$ trial during acquisition in premenstrual and control women.

(Figure I, middle panels). During the test trial, in the acquisition phase, more PM-women tended to react with a response ($\chi^2 = 2.57$, $0.05 < p < 0.10$) than did C-women, and they tended to do so with a greater reaction (PM = 0.600; C = 0.280; $0.05 < p < 0.10$) (Figure II).

Extinction is not complete as long as a reaction to CS$^+$ is greater than it is to CS$^-$ slides. This is reflected in the significant Stimulus x Trials interaction ($F(9,261) = 2.03$). Post-hoc t-testing showed that this difference occurred only in the PM-group (Figure I, right panels). Another indication of the delayed extinction in the PM-group was the slight Group x Stimulus interaction ($F(1,29) = 3.22$; $0.05 < p < 0.10$).

Discussion

Data obtained are in line with those reported by Asso and Beech (1975) and Vila and Beech (1977) and they partly confirm our hypothesis. The acquisition of a classically conditioned skin conductance response was facilitated in pre-menstrual women as compared to women in all other phases of the menstrual cycle.

Though there was a significant difference between groups during extinction, this finding should be considered with some caution. Reactions to CS^+ during acquisition did initially increase in C-women; however, reactions to CS^- also followed the same course (Figure I). Therefore, one can hardly speak of acquisition of conditioned responses. This is in contrast to PM-women, who showed an increased reaction to CS^+ while conditioned response to CS^- decreased. The difference between the two groups during extinction can probably be explained by the simple fact that PM-women readily acquired a CR while C-women did not. Extinction in the PM-group did not occur immediately after the end of the acquisition phase, so that comparison of extinction between two groups is quite difficult and the question of delayed extinction remains as yet unresolved.

Differences emerge for the first time during acquisition. Why were PM women readily conditioned to respond and C women not? There were no striking differences that could account for this effect. The shock level was the same in both groups, so that the difference in reactions between the PM and C-groups cannot be explained by a difference in the intensity of the aversive stimulus. Neuroticism was also as high in the PM-women as in the C-women. Thus, this particular psychological factor cannot have contributed to the facilitated conditionability of women in the pre-menstrual phase. Both PM and C-women behaved the same during habituation. This means that women in both groups did not differ in orientation reaction to the presentation of the slides. An other possibility could be the salience of the slides. However, slides were clearly recognizable pictures, with CS^+ and CS^- equally balanced across groups. An important point to note is the intensity of the UCS. The UCS might have been not sufficiently aversive, for strong conditioning to take place. As compared with the values reported by Tursky (1976), on the relationship between pain and electric shock, the intensities used are in between the "motivated" and "unmotivated upper threshold". But we can only speculate about this effect since in comparable studies (conf. Öhman and associates) no data about shock intensities have been reported.

To summarize, there is no experimental reason why, women in this phase of menstrual cycle are more likely to form aversive associations. So the particular bodily state is probably the responsible underlying mechanism that facilitates acquisition of fear and inhibits its extinction. These data add to the assumption that physiological state is a major determinant in the development of emotional disorders. The heightened susceptibility to phobic fears that returns each month, may thus account for the high incidence of female phobic responses.

3.4
EXPECTANCY EFFECTS ON RESPIRATION
During lactate infusion

G.M. van der Molen & M.A. van den Hout.
Psychosomatic Medicine (in press).

Abstract

The effect of lactate infusion on pCO_2 and respiration rate was studied in two differently instructed groups of healthy volunteers in a double-blind, placebo-controlled cross-over study. Both groups showed a significant decrease in alveolar pCO_2 after lactate but not after placebo. This was accompanied by an increase in respiration rate in those subjects who had expected to become anxious and by a decrease in respiration rate in those who had expected to experience pleasant excitement.

Introduction

There is mounting evidence that panic is often accompanied by hyperventilation (HV), producing a hypocapnia and a respiratory alkalosis. The relationship between these phenomena has become a much debated issue. When instructed to overbreathe, the majority of panic patients experience physical symptoms which they rate as identical to those of clinical panic (Garssen et al., 1983; Bonn et al., 1984; Clark et al., 1985; Salkovskis & Clark, 1986) Other authors reported that slight acidosis, produced by 5%CO_2 inhalation is more anxiogenic than HV (Gorman et al., 1984). Most panic research, however, has relied on lactate infusion studies. Sodium lactate elicits panic in the majority of patients but not in normals (Pitts & McClure, 1967; Margraf et al., 1986). Whereas HV produces a respiratory alkalosis, in sodium lactate infusion a metabolic alkalosis is present, and a compensatory hypoventilation may be expected.

To the best of the authors' knowledge, in only two lactate studies was respiration rate (RR) measured (Bonn et al., 1971; Freedman et al., 1984) and in only one was pCO_2 measured (Liebowitz et al., 1985). From the Bonn et al. study (1971), the authors concluded "... that lactate-infusion is not associated with hyperventilation" (p. 469), yet no exact data on ventilation or RR were presented. In the Freedman et al. study (1984), differen-

ces in RR were found neither between normals and patients nor between lactate and placebo. Liebowitz et al. (1985) demonstrated a pCO_2 decrease after lactate infusion, both in normals and in patients. This decrease was more pronounced in those subjects who had panicked. The authors attributed this effect to HV in those subjects.

If indeed subjects who become anxious during sodium lactate infusion would simultaneously start hyperventilating, a HV-induced respiratory alkalosis would be superimposed upon the metabolic alkalosis resulting from sodium lactate metabolism. The physical symptoms of the infusion would become much more pronounced.

Hypothesizing that in anxious subjects HV would occur, and not in non-anxious subjects, the authors infused both placebo and sodium lactate in normal volunteers without anxiety complaints. Their infusion anxiety was manipulated by pre-infusion instructions. Both RR and pCO_2 were registered.

Method

Thirteen healthy male paid volunteers received a sodium lactate infusion (500 mm d,l-Lactate; 10 ml/kg body weight in 20 min.) and placebo in a double-blind cross-over study. Seven of them were told that the infusions might cause unpleasant bodily sensations similar to those experienced during periods of anxiety and that they might experience anxious affect. Six were told that infusions would evoke feelings of "pleasant excitement", such as those experienced while participating in sports, watching an exciting movie, etc.. Alveolar pCO_2 and RR were measured for about 2 minutes, immediately before and after each infusion. pCO_2 was measured by means of a Could Godart Mark IIR capnograph, using a face mask. RR was inferred from the capnogram. To evaluate mood changes participants rated their subjective states on a visual analogue scale, rating from -100 (very anxious tension) to +100 (very pleasant excitement).

Results

The procedure for manipulating anxiety proved effective. No mood changes were reported in the placebo condition. However, during the lactate infusion, those subjects who had received "anxious instruction" experienced a significant increase in distress while those who had received "pleasant excitement instruction" did not (Van der Molen et al., 1986). The number of reported physical symptoms during lactate were the same for both groups

(8.1 and 7.6, respectively) while hardly any symptoms were reported during the placebo infusion. Data for pCO_2- and RR-changes are represented in table 1.

TABLE 1. Changes in pCO_2 and RR After Lactate and Placebo Infusions in Two Differently Instructed Groups

	pCO_2 change (mmHg)		RR change (cycl/mi	
	After lactate	After placebo	After lactate	p
Anxiety instruction	−4.95	0.95	+2.01	
Pleasant instruction	−3.26	−0.83	−1.23	

Table 1: Changes in pCO_2 and RR after lactate and placebo infusions in two differently instructed groups.

As for the pCO_2 data, analysis of variance (ANOVA) revealed a significant factor Infusion ($F(1,11) = 11.11$; $p < 0.01$) indicating that the procedure had been effective: hypocapnia was induced in both groups during lactate but not during placebo (Figure I, left panel). Subjects in the anxious condition showed a greater drop in pCO_2 than did the subjects in the pleasant excitement condition ($t = 2.45$; $p < 0.05$).

ANOVA on RR revealed no significant main effect, but Infusion x Instruction reached significance ($F(1,11) = 5.13$; $p < 0.05$), reflecting no changes during placebo but a RR increase in anxious subjects and a RR decrease in non-anxious subjects (Figure I, right panel).

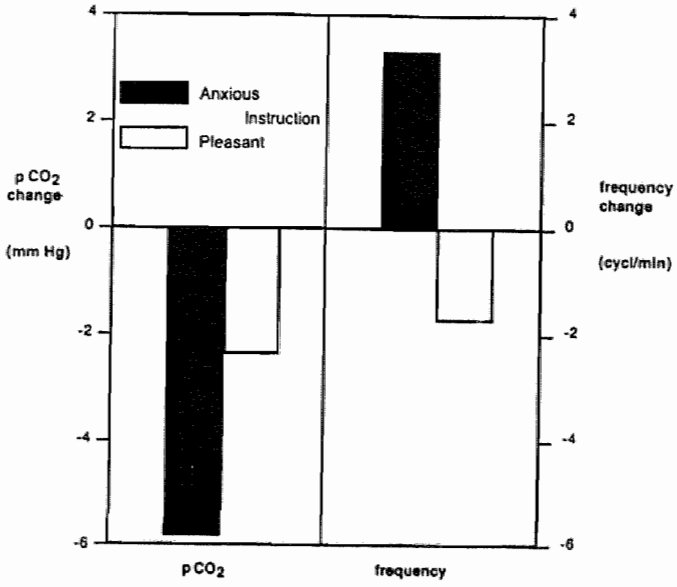

Figure I: Changes in pCO_2 and RR after lactate infusion in two differently instructed groups. Bars represent the difference between lactate and placebo values.

Discussion

Both groups showed lowered pCO_2 during lactate infusion but not during placebo. During lactate, the anxious instruction group reported a significant anxiety increase while

the other group did not. In the anxious group, 6 of the 7 subjects showed an increase in RR while, in the other group, lactate induced a drop in RR in 5 out of 6 subjects. The increase in RR in the anxious group probably points to hyperventilation. This is in line with Liebowitz et al.'s observations (1985) that lactate-induced pH increases are greater in panicking patients than in normals. Though respiratory parameters were not measured, Liebowitz et al. (1985) infer that panic patients may have been hyperventilating during lactate challenge.

Data from the present study show that lactate infusion can result in a RR increase or decrease, depending on the occurrence of lactate induced anxiety. Self-report studies show that panic patients express fear of the very physical sensations that occur during lactate infusion (Van den Hout, Van der Molen et al., 1987). Thus, lactate may be anxiogenic in panic patients because it produces feared sensations, thereby triggering interoceptive anxiety. Ackerman and Sacher (1974) were the first to suggest that lactate induces panic by misinterpretation of somatic sensations. It is of current interest that the degree to which anxiety produced by other anxiogenic agents, such as 50%CO_2 inhalation (Rapee et al., 1986) or HV provocation (Margraf et al., 1988), in panic patients can be dramatically influenced by cognitive manipulations prior to the CO_2 or HV test. Taking into account that negative associations are easily acquired when interoceptive stimuli are involved (Razran, 1961), the fact that our subjects in the anxious condition - and they alone - reacted to metabolic alkalosis with a RR increase, and pCO_2 drop greater than the subjects in the non-anxious condition, may be attributed to instruction-induced anxiety. These healthy normal subjects reacted with a drop in pCO_2 (5.90) comparable to the drop in pCO_2 of the patients who panicked (5.86) in the Liebowitz et al. study (1985). The pCO_2 drop in the non-anxious group (2.43) is the same as in the control subjects (2.39) of the Liebowitz et al. study (1985). Studies aimed at cognitive processes in lactate challenge involving not only normal controls, but also panic patients, should be welcomed.

In the present study, only a small number of subjects was involved. We did not record blood pH or respiratory minute volume. So results must be viewed with some caution. Still, the data suggest that anxiety during lactate infusion leads to a counterregulatory respiration pattern that increases the lactate metabolism induced drop in pCO_2 and rise in pH. Further experiments that control for pH and total ventilation, and that measure the intensity of the sensations that subjects experienced may eventually shed more light on the intriguing issue of lactate induced anxiety.

3.5
THE EFFECT OF HYPOCAPNIA AND RESPIRATORY ALKALOSIS ON ACQUISITION

And extinction of conditioned electrodermal responses

Summary

Acute non-situational panic is a core characteristic of panic disorder but seems to predispose to, or to occur in combination with situational anxiety such as agoraphobia. Literature on experimental panic provocation suggests that a systemic alkalosis might play a role in the genesis of agoraphobia. It was hypothesized that when a subject is in a state of respiratory alkalosis, the acquisition of classical conditioned anxiety is facilitated and/or the extinction is inhibited. In a differential classical conditioning paradigm, consisting of a habituation-, an acquisition-, and an extinction-phase, slides and electric shock were used as conditioned stimuli (CS) and unconditioned stimuli (UCS) respectively. The skin conductance response was taken as (U)CR. Subjects were randomly assigned to two groups: hyperventilation or control. In the first experiment a respiratory alkalosis was induced during the acquisition phase, in the second experiment a respiratory alkalosis was induced during the extinction phase. When subjects are in a state of hypocapnia during the acquisition of conditioned fear, the acquisition is not facilitated and the extinction is not delayed. Nor is the extinction inhibited when subjects are hypocapnic during the extinction. These data support the view that physiological changes as such are not a sufficient condition in the acquisition and maintenance of neurotic fears. Data of the present study add to the validity of a cognitive-physiological interpretation of panic.

Introduction

Spontaneous panic attacks and agoraphobia seem to be closely related. The majority of patients diagnosed as suffering from panic disorder experience at least some avoidance, while most of agoraphobics mention that their avoidance started with a series of panic attacks (Franklin, 1987). The question is raised why specifically panic attacks often occur in combination with, or seem to predispose to situational anxiety, such as agoraphobia. Literature on experimental panic provocation and on hyperventilation provide some interesting suggestions.

First, intense anxiety is common in the hyperventilation syndrome (HVS), and profound hyperventilation (HV) plays a role in maintenance of complaints in approximately 2/3 of agoraphobic patients (Garssen et al., 1983). Symptoms characteristic of the HVS are, at least partly, the result of hypocapnia and a respiratory alkalosis (Gelder, 1985). When asked to voluntarily overbreathe the majority of panic patients experience physical symptoms and negative affect, which they rate as similar to the experience of clinical panic (Bonn et al., 1984; Clark et al., 1985; Salkovskis & Clark, 1986).

Second, a comparable phenomenon occurs in experimental panic-provocation interventions, such as lactate infusions (Pitts & McClure, 1969; Liebowitz et al., 1984, 1985; Margraf et al., 1986) and bicarbonate infusions (Grosz & Farmer, 1969, 1972). The experimentally induced metabolic alkalosis is accompanied by a number of physical symptoms typical of anxiety, such as palpitations, dyspnea, dizziness, etc. Most panic patients react with extreme anxiety to these triggers while normals do not.

Finally, a fair amount of research has also been done on the relationship between the effects of inhalation of a 35%CO_2-65%O_2 mixture and panic (Griez et al., 1987; Fyer et al., 1987). Inhalation of this mixture reliably induces panic symptoms comparable to those of lactate infusions or of HV provocation and also elicits high anxiety in panic patients. Somewhat paradoxically, the physical sensations do not occur during the initial hypercapnia but during the subsequent pCO_2 drop and hypocapnia that follows the 35%CO_2 challenge (Van den Hout & Griez, 1985).

To summarize, there are three reliable experimental procedures for eliciting anxiety and panic symptoms under controlled conditions, all of which have a systemic alkalosis, reflected in lowered pCO_2, in common.

Some researchers suggest that the panic attack can act as an unconditioned, aversive, stimulus (UCS) and that stimuli, such as public places, can become conditioned stimuli (CS) (Eysenck, 1968). Agoraphobia could thus be explained by classical conditioning. Considering the close relationship between panic attacks and agoraphobia on the one hand, and the systemic alkalosis as a characteristic feature of panic on the other, it was hypothesized that an alkalosis in itself might play a causal role in the genesis and/or maintenance of situational anxiety: the acquisition of situational fear may be facilitated and extinction of situational fear may be inhibited by hypocapnia and alkalosis.

Considering that Pavlovian approaches to situational anxiety have proved rather successful, it was decided to use a classical conditioning paradigm to test the issue under review. The set up was a differential conditioning design comparable to the one commonly

used by Öhman and co-workers (Öhman et al., 1976; Öhman, 1986). Physiological factors were varied. Two groups, one in a state of hypocapnia and one in a state of normocapnia, are exposed to different pictures one of which has been consistently reinforced by an electric shock, whereas the other one never has been reinforced. We were interested in pure alkalosis effects on conditioning, while the possibility that alkalosis induces fear in some subjects and that this fear interferes with conditioning, was outside the present scope. Therefor we pre-tested all subjects for fear during respiratory alkalosis and those subjects expressing fearfulness during pre-test did not participate in the experiments. Since there is ample evidence of skin conductance response (SCR) as an index of anxiety, this measure was used as dependent variable.

It was hypothesized that, when subjects are in a state of respiratory alkalosis, during the acquisition of classically conditioned SCR this acquisition will be facilitated, and that the subsequent extinction of that SCR will be delayed (experiment I). It was also hypothesised that in subjects in a state of respiratory alkalose the extinction will be delayed (experiment II).

Experiment I
HYPOCAPNIA DURING ACQUISITION

Method

Subjects

The subjects were 32 undergraduate students (9 males and 23 females) with no current or prior history of phobic complaints. Their age ranged from 19 to 34 years. Subjects were paid for their participation in the study. They were randomly assigned to one of the two groups: hyperventilation during acquisition (HV-group) or control (C-group).

Before the actual experiment, subjects filled out two questionnaires. The first questionnaire was the Dutch version of the State-Trait-Anxiety-Inventory (STAI) (Van der Ploeg et al., 1981) to measure general anxiety level. The second was the "Nijmegen Questionnaire" (NQ), a 18-item inventory to measure the possible presence of the Hyperventilation Syndrome (Van Dixhoorn & Duivenvoorden, 1985).

Apparatus and stimulus materials

SCR and skin conductance level (SCL) were recorded with a Beckman Skin Conductance Coupler (type 9844), using the method of constant voltage (0.5 volts). The coupler allowed for a maximum sensitivity of 0.05 micromho. Beckman Ag-Agcl electrodes (diameter = 8 mm), were attached with adhesive collars to the distal phalanges of the second and third fingers of the left hand.

An electric stimulator with a maximum capacity of 60 mA delivered an electric current (dc) to the subjects. Two shock electrodes were placed on the first finger of the subject's left hand, at the distal and medial phalanges.

The CS's consisted of slides depicting a crowd and moving staircases. A Kodak Carousel was used for presentation of the slides. The slides were projected onto a white wall. The size of the projected image was approximately 80x120 cm, 2.5 m in front of the subject. Onset and offset of the stimuli, inter-trial intervals, occurrence of the electric pulses and response registration were controlled by a microcomputer (PDP Minc-11).

End-alveolar carbondioxide pressure (pCO_2) was measured continuously by means of a Gould Godart Mark-IIR capnograph.

Design

A 2 (group) X 2 (reinforcement) factorial design with repeated measures on the last factor was used. For statistical analyses, a trial factor, in the form of a repeated measure, was added. The group factor refers to the condition the subjects were assigned to: HV or C. The reinforcement factor is a consequence of the fact that each subject saw two slides, one of which (CS^+) was during the acquisition phase associated with electric shock (UCS) and the other (CS^-) never being followed by an UCS.

Procedure

Subjects in the HV-condition came to the laboratory a few days prior to the actual experiment proper. They were fully explained what HV is and what they could expect. Then the experimenter demonstrated how to ventilate very forcefully and subjects were trained in reducing their pCO_2 rapidly and how to keep it reduced to 50% of their resting pCO_2. Finally they were instructed to recuperate quickly. Most subjects could meet the criterium without difficulties in one training session. Subjects who could not and those experiencing anxiety during HV provocation were excluded from the actual experiment. Subjects in the control condition also came to the laboratory a few days before the actual experiment.

They were "trained" to do a mental arithmetic task for two minutes followed by a handtapping task. These tasks were chosen to control for distraction and motoric activity comparable to the experimental group.

Some days after the training session subjects came to the laboratory for the conditioning procedure. Upon arrival in the laboratory, subjects were asked to sit down in a comfortable chair which was placed in a dimly lit, sound attenuated chamber. Recording apparatus, microcomputer and Kodak Carousel were in an adjacent room. The slides were projected through a hole in the wall. The experimenter then explained that during the experiment electric shocks would occur. After subjects had given their consent and electrodes had been fastened, the experimenter started a shock work up procedure in which the shock level was gradually increased until the subject indicated that the shock was "very uncomfortable but not painful". Subjects were not instructed about the CS-UCS contingency.

The experiment consisted of three phases. The first was a habituation procedure. This phase involved 8 CS-only trials (4 CS^- and 4 to be CS^+). Before the start of the second, acquisition phase subjects in HV-condition were asked via intercom to HV forcefully for two minutes reducing pCO_2 to circa 1/3 (or lower) of the resting pCO_2 and then to lower the frequency and/or depth of ventilation so that pCO_2 was reduced to 50% of resting value. At that point the experimenter gave feedback of their performance and subject were asked to keep ventilation continuously at that rate/depth, as was learned in the training session. (Subjects in C-condition were at this point asked to do the mental task and to start hand-tapping). Then the procedure continued and the acquisition phase followed, in which 6 reinforced presentations of CS^+ and 6 unreinforced presentations of CS^- occurred. At the end of this phase subjects were asked to breath at own pace, or to stop hand-tapping respectively. Finally, there was an extinction phase, consisting of 10 unreinforced presentations of both slides.

Slides were presented for 8 sec. The duration of the shock was 0.5 sec and it was delivered exactly upon removal of CS^+. Inter-trial intervals varied between 20 and 40 sec, in steps of 5 sec, and with a mean of 30 sec. Throughout the experiment, the order of presentation of the two slides was quasi-random; no more than two successive presentations of the same slide occurred. CS^+ and CS^- slides were counterbalanced across the two groups.

Response definition and analysis

An 8 second CS-UCS interval allowed for the recording of multiple response forms of the SCR (Prokasy and Kumpfer, 1973). Like Öhman et al. (1976), differentiations were made between FAR-, SAR- and TOR-components of the SCR. The FAR (first-interval anticipatory response) pertains to a maximal deflection with a latency of 1-4 sec after CS onset. The SAR (second-interval anticipatory response) is defined as a maximal deflection at 4-8 sec after CS onset. Maximal deflections occurring at 1-4 sec after CS offset during the habituation and extinction phases are regarded as TORs (third-interval omission responses). The SCR components were measured in micromho and square-root transformed (Venables & Christie, 1973). Data were analyzed as response magnitudes.

Separate analyses of variance were carried out for FARs, SARs and TORs during the three phases of the experiment. The comparisons of interest are a group x reinforcement (GxR) interaction during acquisition and/or extinction and a group x reinforcement x trials (GxRxT) interaction during extinction. A rejection level of p.05, with Greenhouse-Geisser corrections was adopted for all comparisons.

Results

The mean of the UCS level was 27.2 mA in HV group and 24.4 mA in control group. This difference did not reach significance. There were also no significant differences in anxiety level, NQ-scores, or initial SCL-levels.

Data on FAR SAR and TOR during the three phases of the experiment are depicted in Figure 1. Mean SCR are represented in blocks of 2 trials, except for the first block in the habituation phases of FAR and SAR which is, due to experimental procedure, a representation of three trials.

Habituation

There was a significant main effect of Trials for FAR ($F(4,120) = 4.92$) and TOR ($F(3,90) = 12,76$), indicating a decrease in SCR over trials. In addition a significant interaction was found for SAR, which was caused by the absence of habituation to the to be CS^+ slides in the HV group. No other effects reached significance in this phase, which was in line with the expectations.

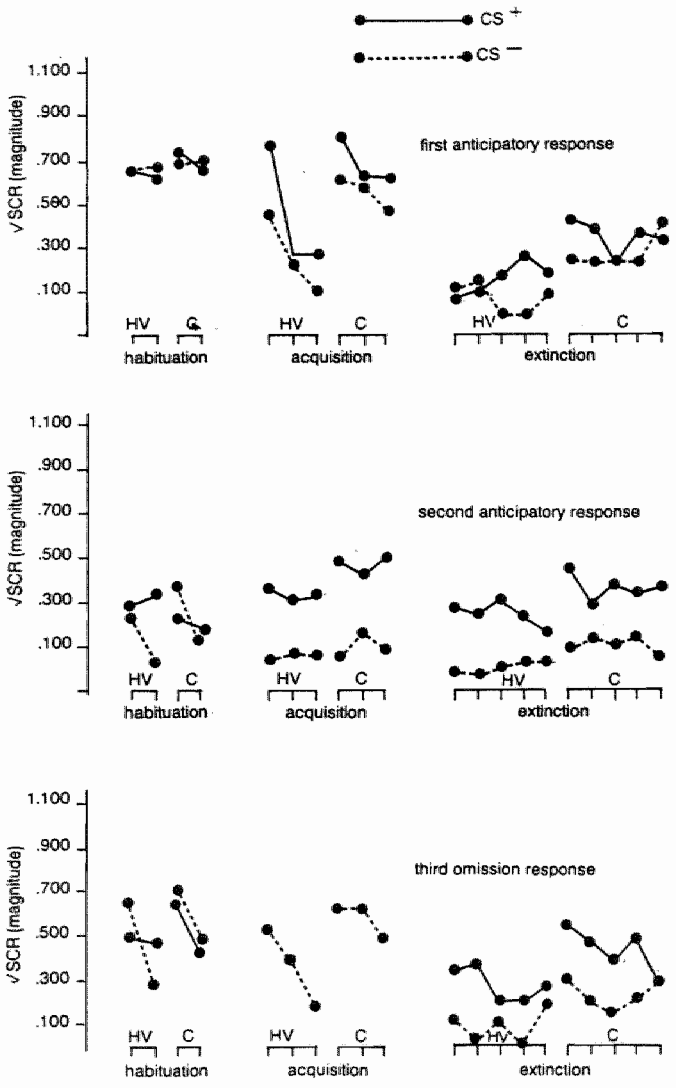

Figure 1. Mean magnitude SCR plotted as a function of trial blocks for the FAR, SAR and TOR to reinforced (CS^+) and nonreinforced (CS^-) stimuli for the Hyperventilation during acquisition (HV) and Control (C) groups.

Acquisition

Figure 1 shows the TOR data from habituation and extinction only, because during acquisition no conditioned response comes up but SCR values represent a direct reaction to the shock. The conditioning procedure was highly effective as is shown by the significant R effects for both FAR and SAR ($F(1.30) = 22.05$ and $F(1.30) = 41.08$, respectively) and a significant RxT interaction for FAR ($F(5.150) = 8.76$). Furthermore no significant GxR interaction emerged. This means that there was no difference in ease of acquisition between the groups.

Extinction

The most outstanding feature of this phase was the maintenance of a strong R effect ($F(1,30) = 10.65$, $F(1,30) = 29.04$ and $F(1,30) = 17.82$, for FAR, SAR and TOR respectively), indicating a reliable CS^+-CS^- differentiation. However, no other significant differences emerged indicating that no significant extinction occurred. Also no GxR or GxRxT interaction was found.

Comment

The obtained data did not confirm our hypothesis that hypocapnic subjects during acquisition would acquire a classical conditioned electrodermal response more easily than normocapnic subjects. Analysis of variance showed that the conditioning procedure was effective but no group x reinforcement interactions emerged, neither during acquisition nor during extinction. No group x reinforcement x trial was found during extinction. So there were no differences between hyperventilating and control groups found.

Experiment II
HYPOCAPNIA DURING EXTINCTION

Method

Subjects were 32 undergraduate students, 10 males and 22 females, 19-24 years of age. Again, subjects were randomly assigned to one of two groups, consisting of hyperventilation during extinction (HV group) or control (C-group).

The apparatus and stimulus materials, the design, the response definition and analyses are all identical to the methods used in the first experiment (see above). The only difference was in the procedure. Subjects performed the HV- or control-task during the extinction phase instead of during the acquisition phase.

The comparisons of interest are now during extinction only. No differences between groups are expected during habituation or acquisition. A group x reinforcement (GxR) interaction or group x reinforcement x trial interaction are expected.

Results

The mean of the UCS level was 26.7 mA in the HV group and 26.4 mA in the control group. This difference did not reach significance. There were also no significant differences in anxiety level, NQ-scores, or initial SCL-level. This difference did not reach significance. Data on FAR, SAR and TOR during the three phases of the experiment are depicted in Figure 2. The mean SCRs are represented as in experiment I.

Habituation

There was a significant main effect Trials for SAR and TOR ($F(4,120) = 4.78$ and $F(3,90) = 5.97$) indicating that habituation occurred in the case of SAR and TOR only. No other effects of interest reached significance in this phase.

Acquisition

Data for FAR and SAR are presented only. A strong main effect Reinforcement was found ($F(1,30) = 42.79$, $F(1,30) = 35.83$ for FAR and SAR respectively), as well as a Trial effect for FAR ($F(5,150) = 3.19$), and a RxT interaction ($F(5,150) = 3.44$, $F(5,150) = 3.19$), for both FAR and SAR. This indicates that the procedure was highly effective and that a reliable differentiation between CS^+ and CS^- took place. No difference between groups or GxR interaction emerged.

Extinction

During extinction significant Reinforcement ($F(1,30) = 6.86$, $F(1,30) = 37.08$, $F(1,30) = 13.83$) and Trial effects emerged. No RxT interaction reached significance, indicating that although responsivity overall decreased differential responding was maintained and thus no substantial extinction occurred. No significant GxR or GxRxT

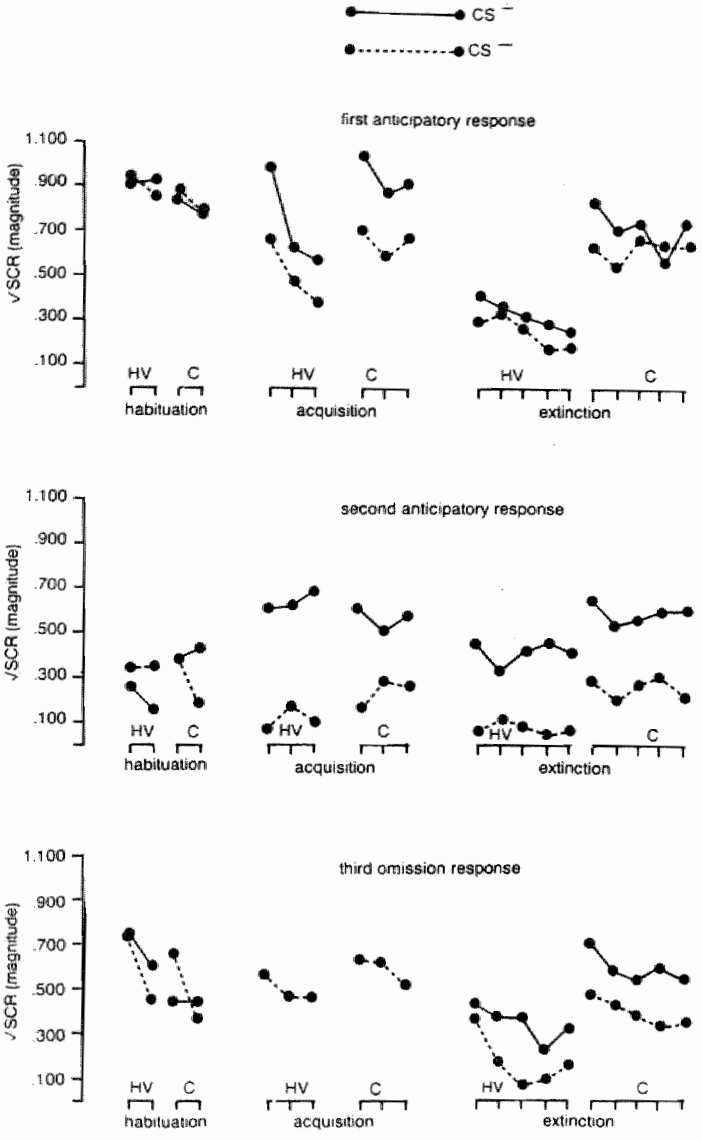

Figure 2. Mean magnitude SCR plotted as a function of trial blocks for the FAR, SAR and TOR to reinforced (CS^+) and nonreinforced (CS^-) stimuli for the Hyperventilation during extinction (HV) and Control (C) groups.

interactions were found, which means that there was no difference in the process of extinction between the groups. An unexpected significant main effect group showed up, ($F(1,30) = 7.52$, $F(1,30) = 6.31$, $F(1,30) = 6.48$) indicating that the SCR in HV-group was overall lower than in the C-group.

Comment

The obtained data did not confirm our hypothesis that subjects in a state of respiratory alkalosis during extinction, will show a delayed extinction of a classical conditioned electrodermal response, as compared to normocapnic subjects.

Unlike the first experiment, HV-subjects had smaller SCR's than C-subjects during their HV-period. However, from the figure can be seen that this effect tended to be present in experiment 1 also. It is possible that this difference is inherent in the HV task. Proper control will consist of "normocapnic hyperpnea". However, there are no a priori reasons to assume that this decreased SCR might have influenced the occurrence of delayed extinction.

General Discussion

In the present study no evidence was found to suggest that resistance to extinction is specific in those subjects who hyperventilated during either the acquisition or the extinction of fear reactions. Also, no evidence was found that the ease of acquisition differed between subjects who hyperventilated and those who did not.

Before speculating about the possible implications of these findings some methodological comments are in order. First, overall there was a strong conditioning effect, both during acquisition and during extinction. This might have possible overruled the effect of hypocapnia. Beside that, it is hard to interpret the extinction data, because in both groups there was hardly any. So it is difficult to decide whether extinction was delayed or not. This is quite contrary to existing literature. In most studies on prepared conditioning 20 extinction trials proved to be sufficient to document differential extinction (see review by Öhman et al., 1978) as a function of stimulus type. However, as the study by Dawson et al. (1986) perfectly makes clear, differential extinction effects as a function of stimulus type become more pronounced when an extensive extinction procedure is used (i.e. 48 instead of 20 trials). It may well be that delayed extinction as a result of hypocapnia only emerges when

an extensive extinction procedure is used. Future research should preferable employ more extinction trials and weak conditioning paradigms, e.g. trace conditioning and low UCS intensities, to prevent such ceiling effects.

A second issue of interest is the differences between the three components of the skin conductance response. The phobic anxiety reaction is often seen by learning theorists as a conditioned emotional response wherein sympathetic activity is most pronounced. Therefore SCR has played a prominent role in experimental anxiety research (Katkin & Deitz, 1973). Nowadays it has become clear, however, that attention and arousal can affect SCR to a considerable extent (Spinks et al., 1985). In the work of Öhman et al. (see: Öhman 1986) mostly FAR was the component of interest. Contrary to what is reported most in this kind of research, in both our experiments, not the FAR, but SAR and TOR show the most pronounced effects. This is in line with the findings of Merckelbach, van der Molen & van den Hout (1987) who also found in a comparable study better conditioning effects for SAR than for FAR. There are theoretical plausible arguments to explain that effect. The FAR has a latency of 1 to 4 seconds after stimulus presentation. The FAR may be considered as an orientation reaction to CS while the SAR, with a latency of 4-0 seconds prior to CS-offset, c.q. expected UCS-onset, can be considered as the anticipation to UCS (Gray, 1981).

Another problem in the present experiment is the extent to which slide-shock parings can be considered as a laboratory model for conditioning processes in agoraphobia. One might question the "belongingness" between the slide content and the shock. To draw again a parallel with the preparedness research, the conditioning study by Cook et al. (1986) has shown that a resistance of extinction to slides of snakes and spiders does only occur when shock rather than white noise is used as the UCS. Thus it is possible that a different UCS (e.g. an interoceptive UCS such as tachycardia) would have facilitated delayed extinction in the present experimental procedure.

Finally, it might be argued that a decrease in pCO_2 to 50% of resting value is hardly ever noted during natural occurring panic. However, this circumstance should have been an a fortiori argument in favor of our hypotheses.

Beside these methodological considerations the question is open why we couldn't we demonstrate an influence of respiratory alkalosis on the acquisition or extinction of fear responses, despite of the close relationship between panic and agoraphobia. Why does specifically a panic attack predispose to agoraphobia and other aversive events do not? A specific biological vulnerability has been suggested to exist in panic patients. The biologi-

cal models of Klein (1981) and Sheehan (Carr & Sheehan, 1984) have been very influential. However, alternative explanation have emerged (Ackerman & Sachar, 1984; Van der Molen & van den Hout, 1987; Clark, 1980), the "cognitive model" of Clark (1986) being the most elaborated to date. These explanations share the opinion that the perception and interpretation of bodily symptoms lead to panic. These models suggests that the development of fear can best be described as a selfmaintaining positive feedback loop. Minor internal stimuli, once felt, are "catastrophically misinterpreted" (Clark, 1986), amplifying in turn the frightening sensations, increasing anxiety and so on. The presence of both bodily sensations and the catastrophical misinterpretation of these sensations is the very crucial point of this model.

The present study sought to isolate the two parts of the process and to investigate the role of alkalosis as such. Therefore subjects were selected who showed no signs of overt anxiety when hyperventilating and thereby producing bodily sensations such as palpitations, tingling hands etc. Subjects indicated afterwards that they had not experienced fear during the experiment, due to HV. According to a cognitive physiological model of panic, the panics that occur in situations when an alkalosis is induced (lactate, bicarbonate, HV-provocation) can be accounted for by the fact that subjects mislabel the sensations accompanied by an alkalosis. To the extent that one can assume that the absence of group differences was not caused by methodological factors, the findings of the present study, that alkalosis as such does not influence the acquisition or extinction of fear, add to the validity of this view.

3.6
COGNITIVE DETERMINANTS IN LACTATE ANXIETY

Summary

G.M. van der Molen, M.A. van den Hout, J. Vroemen, H. Lousberg & E. Griez. Behaviour Research and Therapy, 24, 677-681, 1986.

The effects of lactate infusion on subjective mood change were studied in two differently instructed groups, in a double-blind, placebo-controlled, cross over study. Subjects who were told that infusions would produce anxiety reported a significant change in the expected direction after lactate but not after glucose. Subjects who were told that infusions would produce a state of pleasant excitement showed no change after either infusion. The possible role of cognitive parameters in experimentally induced anxiety is discussed.

Introduction

A good deal of research on panic disorder has focussed on experimentally induced anxiety. The effects of biological agents such as sodium lactate (Guttmacher et al., 1983; Liebowitz et al., 1984; Liebowitz et al., 1985) and CO_2 (Gorman et al., 1984; Van den Hout and Griez, 1984; Griez et al., 1986) are rather well documented: the majority of patients panic on these challenges while normals do not. The underlying mechanism, however, is not yet clearly understood. A specific biological vulnerability has been suggested. The biological models of Klein (1981) and Sheehan (Carr and Sheehan, 1984) are the most fully elaborated to date and have been very influential.

The lactate and CO_2 data are also compatible with psychological perspectives on panic (Ackerman and Sachar, 1974; Clark, 1986; Margraf et al., 1986). These other explanations are less developed, yet all seem to share the premise that the perception of bodily sensations can lead to panic. This "cognitive approach" of anxiety holds that "catastrophic misinterpretations of bodily sensations" play an important role in the genesis and maintenance of panic (Beck et al., 1985; Clark, 1986). These cognitive variables are seldom considered in the explanation of experimentally induced anxiety. Many of the physiological and biochemical changes induced by lactate infusions (Liebowitz et al., 1985) can be perceived and, following the cognitive perspective, may be misinterpreted by the panic patients. Thus,

an anxiogenic misinterpretation of lactate induced interoceptions would, at least partly, explain why most patients panic on lactate while normals do not. In earlier lactate studies, experimental expectations based on pre-infusion instructions may have increased the likelihood of such misinterpretations: "Patients were told that they might experience a panic attack and knew basically what to expect. Controls, too, were told that they might experience an attack with symptoms analogous to those of public speaking..." (Appleby et al., 1981).

In this study we explored the relative contribution of cognitive-instructional variables to the occurrence of lactate induced anxiety. We hypothesized that affective responses to lactate can be manipulated by experimental instruction. Subjects receiving lactate after being warned of possible anxious effects ("anxious tension" instruction) were expected to report considerably more distress than those receiving lactate after being given pleasant expectations ("pleasant excitement" instruction). The presence of physical symptoms is considered to be crucial for the occurrence of panic. Therefore no mood change was expected to occur under either condition when a placebo was given.

Method

Subjects

Thirteen healthy male volunteers without any prior or current psychiatric complaints participated in this study. The mean age was 21.6 years and the range was between 19 and 24 years. Before participating subjects filled in the Dutch version of the State-Trait Anxiety Inventory (STAI).

Procedure and design

Sodium-lactate (500 mM d,l-lactate) and a placebo with the same osmolarity (555 mM glucose in 167 mM NaCl) were given to each of the participants (10 ml/kg body weight, in 20 minutes) on two different days. The order of intake was randomly varied.

Both the experimenter and the subjects were blind to the infusions that were given on each day. The time interval between the two infusions was (at least) three days. Subjects were randomly assigned to the "anxious tension" instruction or to the "pleasant excitement" instruction. The design is depicted in Figure 1.

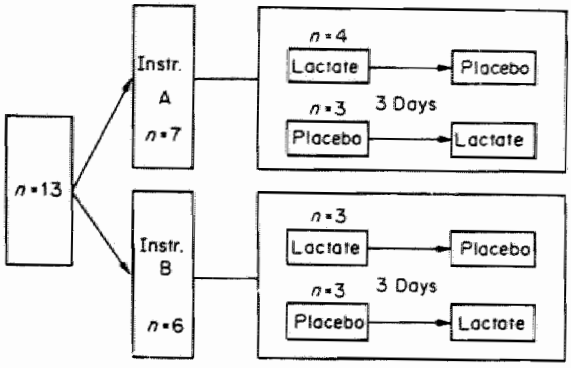

Figure 1 Procedure

Instruction

Subjects in Group A ("anxious tension") were told that the infusions might cause unpleasant bodily sensations similar to those experienced during periods of anxiety. They were also told that they might experience anxious affect. Subjects in Group B ("pleasant excitement") were told that the infusions would evoke feelings of "pleasant tension", such as those experienced after sporting, watching an exciting movie, etc. In both groups it was stressed that the infusions were completely harmless and that the sensations would quickly subside after termination of the infusion. Subjects were also told that, if need be, infusions could be stopped upon their request.

In order to evaluate any mood changes that may have occurred, participants rated their subjective states on a visual analog scale, ranging from -100 (very anxious tension) to + 100 (very pleasant excitement). All subjects were instructed to score their mood change using their pre-infusion affective state -"point-zero" on the scale- as a point of departure. The experimenter made it clear that they had to rate their subjective feelings and not the intensity of the physical sensations.

Results

Mean scores on the scale for subjective mood change are given in Table 1.

	Instruction	
	Anxious	Pleasant
Infusion		
Lactate	Mean = −64.3 SD = 23.9	Mean = +2.7 SD = 46.3
Placebo	Mean = +5.2 SD = 13.9	Mean = +6.6 SD = 11.3

Table 1: Mean scores on the scale for subjective mood change.

Instruction induced expectations had no effect on mood change when a placebo was given. Subjects in Group A and Group B differed in their reaction on lactate ($t = 3.35$, $p < 0.05$). After receiving lactate-infusion and an anxious instruction, a significant increase in anxiety occurred ($t = 9.06$, $p < 0.001$). Those who expected pleasant excitement showed a slight and non-significant rise in pleasant excitement (Figure 2).

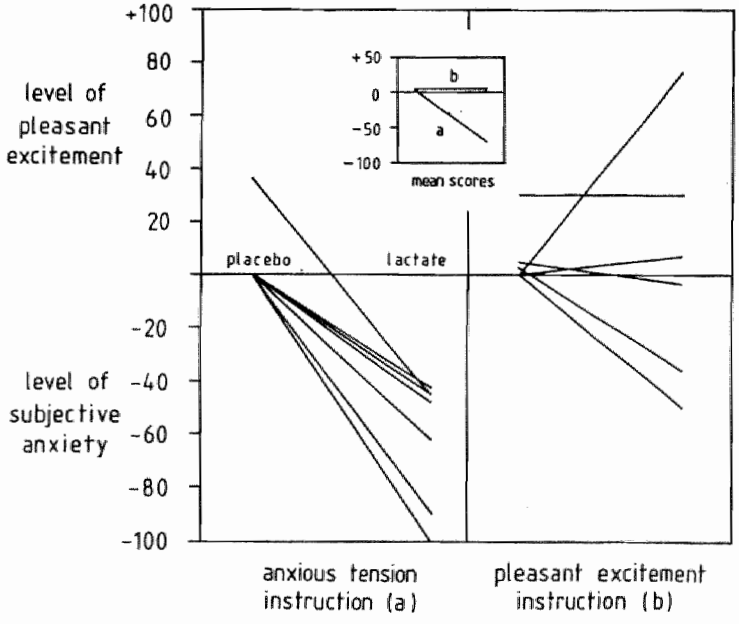

Figure 2: Lactate-induced affect in two differently instructed groups.

Subjects in Groups A and B did not differ in pre-experimental general anxiety level as measured by the STAI ($M(A) = 32.6$, $M(B) = 33.8$; $t = 0.24$,n.s.).

Three-way analysis of variance with instruction (anxious tension vs. pleasant excitement) and order (placebo first vs. lactate first) as between subjects factors and infusion (placebo vs. lactate) as within subjects factor, revealed that no carry-over effects occurred.

Discussion

The data obtained support the hypothesis that the participants' subjective state was more affected by expectation after lactate than it was after the placebo, and that response to lactate can indeed be manipulated by experimental instruction. Subjects who receive "anxious tension" instructions do experience more distress than those who receive "pleasant excitement" instructions. These results are in line with earlier findings from a 35%CO_2 study (Van den Hout and Griez, 1982).

Subjects did not show any mood changes in either condition when a placebo was given. This shows just how important the presence of physical symptoms is for the existence of panic. This in line with Ley's (1985) findings that patients report bodily changes before they panic.

The effects of lactate were very pronounced in the "anxious tension" group. It is quite interesting to note that all seven subjects in Group A reported a considerable increase in anxiety and showed overt signs of anxiety. One subject reported intense panic and requested termination of the infusion. These data lead to the conclusion that not only patients but also "normal" control subjects can become highly anxious with lactate infusion when that is their expectation. Therefore, instructional variables have to be considered when differences between panic patients and control subjects on panic provocation are to be explained.

In Group B the effects were rather complex. Only two subjects reported a moderate increase in anxiety. Three subjects actually reported pleasant excitement and one mentioned pleasant sensations initially but reported some anxious feelings at the very end of the infusion (Figure 2). This would seem to indicate that sodium lactate is probably not an agens that changes general arousal level in such a way that sensations can be labeled in any direction (cf. Schachter, 1964). Therefore, biological factors in experimental panic provocation can probably not be ruled out. Lactate vulnerability may, at least in part, be due to

psychological processes and experimental instructions in lactate studies are crucial to the occurrence of anxiety. Therefore, we would suggest that interaction between physiological changes, and situative cues and cognitive set, can offer an alternative explanatory model.

In order to explore the explanatory power of psychological approaches to clinical panic, this study should be replicated with panic patients. If cognitive factors are to be considered important determinants of panic, it should be possible to considerably reduce the number of panicking patients on lactate challenge when reassuring pre-infusion instructions are given. More empirical data should help to clarify the intriguing phenomenon of experimental panic.

CHAPTER FOUR

CONCLUSIONS AND DISCUSSION

The main goal of this study was to specify the role of intra-subject variables in the etiology and maintenance of anxiety. Concerning the hypotheses formulated in chapter 2.2 and in view of the experiments discussed in chapter 3, the following can be concluded.

1.

The hypothesis that early actual separation from parents predisposes people specifically to agoraphobia or panic disorder (APD) was not confirmed. Both APD and non-panicking neurotic controls (NPNC) tended to have experienced a more disturbed parental environment than normal controls (NC).

2.

The hypothesis that separation anxiety specifically predisposes people to APD, was not confirmed either. While it was found that NPNC scored higher than NC, APD could not be identified as different from either NPNC or NC.

3.

The hypothesis that external orientation as measured with the Rotter IE-scale, is specific to APD was not confirmed. While it was found that APD did not score higher on the

IE-scale than the NPNC group did, both neurotic samples displayed a more external orientation than the normal control group did.

4.

During lactate, subjects who had expected to become anxious showed an increase in respiration rate and a greater decrease in pCO_2 as compared to non-anxious subjects, who showed a decrease in respiration rate.

5.

The fifth hypothesis was partly confirmed. The acquisition of a classically conditioned skin conductance response was facilitated in women in their pre-menstrual phases as compared to women in all other phases of the menstrual cycle. The question of delayed extinction remains as yet unresolved.

6.

Subjects in a state of respiratory alkalosis during acquisition did not acquire a classically conditioned electrodermal response more easily than normocapnic subjects.

7.

Subjects in a state of respiratory alkalosis during extinction, do not show a delayed extinction of a classically conditioned electrodermal response, as compared to normocapnic subjects.

8.

Subjective mood can be affected by instruction prior to lactate infusion but not to placebo condition: the response to lactate can be manipulated by experimental instruction.

Summarizing, it is seen that support is found for the cognitive-physiological approach outlined in chapter two. An alkalosis as such is not a sufficient condition for a facilitated acquisition of neurotic fears, neither is a negative cognitive set alone. The combination of physiological sensations and an anxiogenous interpretation is an important determinant factor in the maintenance of panic.

Before accepting this cognitive-physiological model as generally valid, a number of

methodological and conceptual points can be noted, implying suggestions for future research. To avoid detailed expatiations upon experimental finesses only some main issues will be covered.

An intriguing topic requiring further investigation is the nature of the physiological sensations that can be the subject of anxiogenous interpretation. Razran (1961) suggests that negative associations are easily acquired when, irrespective which, interoceptive stimuli are involved. More specifically, Evans (1972) argues that the sensations that are part of the anxiety response must be involved. Experiments in which different interoceptive sensations are manipulated experimentally, for instance by (false) feedback, may elucidate this issue.

Second, some questions are raised concerning the conditioning paradigm used. Though this paradigm is generally accepted and often used, the choice of electric shock as UCS can be subjected to some criticism. There is no intrinsic relationship between the CS used and electric shock. Though the Pavlovian theory predicts the association between any aversive stimulus and neutral stimuli, and we did, indeed, find a strong conditioning effect, the notion of belongingness should not be neglected (McNally, 1987). A more "fear-relevant" UCS will be used in future research.

The research subjects constitute another possible source of complications. Discrepancies may arise when "normal" healthy volunteers participate instead of panic patients. Our conditioning studies were carried out with normal controls only. Repeating the conditioning experiments with panic patients could add to the understanding of pathological anxiety. Patients might be more easily conditioned than "normal" subjects, irrespective of the presence of alkalosis. Furthermore, the experiments adding to the validity of the cognitive-physiological approach of panic, were all aimed at the induction of anxiety. Both experimental studies using normals (Van der Molen et al., 1986) and patients (Margraf et al., 1988; Rapee et al., 1986) showed that anxiety revives under conditions inducing a negative cognitive set. The next thing to do is to show that anxiety in panic patients can be reduced by the use of cognitive interventions.

Finally, it is possible to influence the effects of pharmacological interventions, such as lactate infusion or carbondioxide inhalations, by well-defined psychological interventions. Therefore the conclusion is forced upon us that the pharmacological models should be explained psychologically. Although our findings suggest that interoceptive fear is a maintaining factor in clinical panic, it would lead us too far to conclude that anxiety is "just" a psychological phenomenon, in which biological explanations are irrelevant. Interesting re-

sults in this matter are reported concerning the effects of yohimbine (an α_2-receptor antagonist) and clonidine (an a_2-agonist). 20 mg of yohimbine produces anxiety and sailliant interoceptions in patients. Normal controls, however, do not report any sensations with this dosage and they are absolutely unable to tell 20 mg yohimbine from placebo, while panic patients easily can (Van den Hout et al., 1988). Moreover, clonidine has a stronger hypotensive effect in panic patients than in normals with identical resting blood pressure (Nutt, 1987). Meanwhile, the anxiogenic effect of yohimbine can be blocked by premedicating patients with clonidine. These observations suggest an impaired noradrenergic regulation in panic patients (Charney et al., 1984; Charney & Heninger, 1986, 1986a).

The question whether panic is either a biologically or a psychologically determined disorder is deceptive. More to the point is the question which observations can best be explained from a biological and which ones from a psychological perspective. The accuracy with which the predictions from our cognitive-physiological model could be confirmed plead in favour of this approach. This approach leaves some questions unexplained, however. Why and by what mechanism is panic triggered for the very first time? Also, the occurrence of nocturnal panic-attacks is an intriguing problem, which is hard to explain from a cognitive-physiological point of view. The effects of yohimbine and clonidine illustrate that a biological approach may be more fruitful in some cases. This question, too, could be a subject for future investigations.

ABBREVIATIONS

APD	patients with panic disorder or agoraphobia with panic attacks
CR	conditioned response
CS	conditioned stimulus
CTA	conditioned taste aversion
DSM	diagnostic and statistical manual of mental disorders
HV	hyperventilation
HVS	hyperventilation syndrome
NC	normal control (subjects)
NANC	non-agoraphobic, neurotic control (subjects)
NPNC	non-panicking, neurotic control (subjects)
pCO_2	partial carbondioxide (CO_2) pressure
pH	the acidity of a solution: negative logarithm of the concentration of H^+ ions
PD	(patients with) panic disorder
PMS	pre-menstrual syndrome
SCL	skin conductance level
SCR	skin conductance response
UCR, UR	unconditioned response
UCS, US	unconditioned stimulus

CONCEPTIONS

Acidosis	a state in which the acidity is higher than normal (decreased pH)
Alkalosis	a state in which the acidity is lower than normal (increased pH)
Hypercapnia	a state of heightened pCO_2
Hypocapnia	a state of lowered pCO_2
Hyperventilation	a breathing pattern in which breathing is stronger than needed for the homeostasis of the body, resulting in lowered pCO_2.

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